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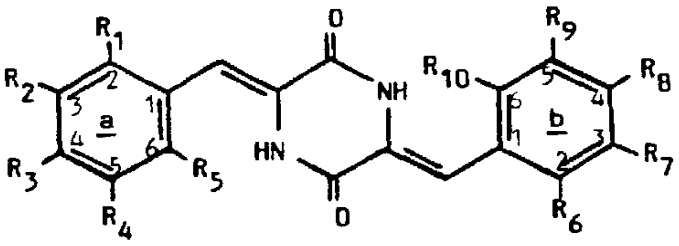
Description

The present invention relates to compounds useful as inhibitors of plasminogen activator inhibitor (PAI), to their preparation and to pharmaceutical and veterinary compositions containing them.

Plasminogen activators (PAs) are serine proteases which control the activation of the zymogen, plasminogen, to the active enzyme plasmin. Plasmin is important in a number of physiological and pathological processes including fibrinolysis, tissue remodelling, tumour growth and metastasis. The glycoprotein plasminogen activator inhibitor (PAI) is an endogenous fast-acting inhibitor of PA activity. PAI is a member of the serpin family and is synthesised by a variety of cells including endothelial cells. An imbalance between PAs and PAI contributes to a number of pathological conditions including haemostasis, inflammation, tumour growth and metastasis.

The present invention provides the use of a diketopiperazine of formula (A):



(A)

wherein each of R_1 to R_{10}, which may be the same or different, is independently selected from hydrogen, C_1-C_6 alkyl unsubstituted or substituted by one or more halogen atoms, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halogen, hydroxy, nitro, optionally substituted phenyl, cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$,$-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ wherein m is 1 or 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ and $-NHCO(CH_2)_nOR^{11}$ wherein n is 0 or is an integer of from 1 to 6, each of R^{11} and R^{12} is independently H or C_1-C_6 alkyl and R^{13} is C_1-C_6 alkyl; or any of R_1 and R_2, R_2 and R_3, R_3 and R_4 and R_4 and R_5, or R_6 and R_7, R_7 and R_8, R_8 and R_9 and R_9 and R_{10}, form together with the carbon atoms to which they are attached a benzene ring which is optionally substituted; or a pharmaceutically acceptable salt or ester thereof; in the manufacture of a medicament for use as an inhibitor of plasminogen activator inhibitor.

The numerals 1 to 10 denote ring positions on the phenyl groups in formula A. The letters a and b refer to the two phenyl rings themselves.

When any two adjacent groups of R_1 to R_{10} form, together with the carbon atoms to which they are attached, a benzene ring, that ring is either unsubstituted or it may be substituted by any of the options specified above for R_1 to R_{10}. The benzene ring forms, together with ring a or b respectively, an optionally substituted naphthalene ring structure.

When ring a or b is substituted phenyl, the benzene ring may be substituted at any of the ortho, meta and para positions by one or more substituents, for example one, two or three substituents, which may be the same or different, independently selected from the groups specified above for R_1 to R_{10} other than hydrogen.

A C_1-C_6 alkyl group is typically a C_1-C_4 alkyl group, for example a methyl, ethyl, propyl, i-propyl, n-butyl, sec-butyl or tert-butyl group. A halogen is, for example, fluorine, chlorine, bromine or iodine. A C_1-C_6 alkyl group substituted by halogen may be substituted by 1, 2 or 3 halogen atoms. It may be a perhaloalkyl group, for example trifluoromethyl.

A C_1-C_6 alkoxy group is typically a C_1-C_4 alkoxy group, for example a methoxy, ethoxy, propoxy, i-propoxy, n-butoxy, sec-butoxy or tert-butoxy group. A C_1-C_6 alkylthio group is typically a C_1-C_4 alkylthio group, for example methylthio, ethylthio, propylthio, i-propylthio, n-butylthio, sec-butylthio or tert-butylthio.

In compounds of formula A free rotation may occur at room temperature about the single bonds connecting rings a and b to the double bonds at positions 3 and 6 of the piperazine-2,5-dione ring. Positions 2 and 6, and positions 3 and 5, in both rings a and b can therefore be considered as equivalent. As a consequence the following pairs of substituents can be viewed as interchangeable: R_1 and R_5; R_2 and R_4; R_6 and R_{10}; and R_7 and R_9.

Preferably one of rings a and b is unsubstituted or is mono-substituted whilst the other ring is unsubstituted or is substituted at one or more of positions 2 to 6. The ring which is mono-substituted may carry the substituent at any one of positions 2 to 6, for instance position 3 or 4, especially position 4. Thus for instance, when ring b is mono-substituted, one of R_6 to R_{10} is other than hydrogen, preferably R_7 or R_8, especially R_8. When ring a is mono-substituted, one of R_1 to R_5 is other than hydrogen, preferably R_2 or R_3, especially R_3. When one of rings a and b is mono-substituted

the substituent R_1 to R_5, or R_6 to R_{10} respectively, is preferably selected from a halogen, for instance fluorine; an alkoxy group, for instance OMe; and an acetamido group -NHAC in which Ac denotes acetyl.

When one of rings a and b is unsubstituted, or is mono-substituted as described in the above paragraph, the other ring may bear any desired substitution pattern. For instance, the other ring may be unsubstituted or may be mono-, di- or tri-substituted at any of positions 2 to 6.

The said other ring may, for instance, be mono-substituted at any of positions 2 to 6. It may also be 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5- disubstituted, or 2,3,4-, 2,3,5-, 2,3,6- or 3,4,5-trisubstituted. Thus, when the said other ring is a and is mono-substituted, four of R_1 to R_5 are hydrogen and one is other than hydrogen. When the said other ring is ring a and is disubstituted, three of R_1 to R_5 are hydrogen and two are other than hydrogen. For example R_1 and R_2, or R_1 and R_3, or R_1 and R_4, or R_1 and R_5, or R_2 and R_3, or R_2 and R_4 are other than hydrogen whilst, in each case, the other three of R_1 to R_5 are hydrogen.

When the said other ring is ring a and is trisubstituted, two of R_1 to R_5 are hydrogen and three are other than hydrogen. For example, R_1, R_2 and R_3, or R_1, R_2 and R_4, or R_1, R_2 and R_5, or R_2, R_3 and R_4 are other than hydrogen whilst, in each case, the other two of R_1 to R_5 are hydrogen.

When the said ring is b and is mono-substituted, four of R_6 to R_{10} are hydrogen and one is other than hydrogen. When the said other ring is b and is di-substituted, three of R_6 to R_{10} are hydrogen and two are other than hydrogen. For example R_6 and R_7, or R_6 and R_8, or R_6 and R_9, or R_6 and R_{10}, or R_7 and R_8, or R_7 and R_9, are other than hydrogen whilst, in each case, the other three of R_6 to R_{10} are hydrogen. When the said other ring is b and is trisubstituted, two of R_6 to R_{10} are hydrogen and three are other than hydrogen. For example R_6, R_7 and R_8, or R_6, R_7 and R_9, or R_6, R_7 and R_{10}, or R_7, R_8 and R_9 are other than hydrogen whilst, in each case, the other two of R_6 to R_{10} are hydrogen.

Alternatively, any two adjacent substituents in the said other ring may, together with the carbon atoms to which they are attached, complete a second benzene ring which is optionally substituted, thus forming an optionally substituted naphthyl group with the said other ring. For instance, in ring a R_1 and R_2, or R_2 and R_3 may form together with carbon atoms 2 and 3, or 3 and 4 respectively, an optionally substituted benzene ring which, in turn, forms with ring a a naphthyl group which is unsubstituted or substituted by one or more groups specified above for R_1 to R_{10}. In ring b R_6 and R_7, or R_7 and R_8 may form, together with carbon atoms 2 and 3 or 3 and 4 respectively, an optionally substituted benzene ring which, in turn, forms with ring b a naphthyl group which is unsubstituted or substituted by one or more groups specified above for R_1 to R_{10}. Typically the naphthyl group in either case is unsubstituted or is monosubstituted at position 1,2,3 or 4 of the naphthalene ring structure, especially position 4. For example R_1 and R_2 together with ring a, or R_8 and R_7 with ring b, form a 4-dimethylamino-1-naphthyl group.

In a preferred series of compounds of formula A each of R_6 to R_{10} is hydrogen. In another preferred series of compounds, one of R_6 to R_{10} is selected from alkoxy, $NHCOR^{11}$ and halogen and the other four of R_6 to R_{10} are H. Alkoxy may be, for instance, OMe or OBu^n. $NHCOR^{11}$ is typically NHAc. Halogen is typically F or Cl. Preferably R_8 is alkoxy, especially OMe or OBu^n; $NHCOR^{11}$, especially -NHAc; or halogen, especially F or Cl; and each of R_6, R_7, R_9 and R_{10} is H.

In the above-mentioned series of preferred compounds R_1 to R_5 are all hydrogen, or one or two of R_1 to R_5 are other than hydrogen whilst the others are hydrogen. For instance one of R_1, R_2 and R_3 is other than hydrogen. Alternatively R_1 and R_3, or R_2 and R_3, are other than hydrogen. Preferred values for the one or two of R_1 to R_5 which is or are other than hydrogen include alkoxy such as OMe or OBu^n, halogen such as Cl or F, hydroxy, $-N(R^{11}R^{12})$, $-CO_2R^{11}$, $-CH_2SCOR^{13}$, $-CH_2SR^{11}$, $-NHCOR^{11}$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-NHCOCH_2OR^{11}$, $-NHCO(CH_2)_nOCOR^{11}$, $-CH_2NHCOOR^{13}$ and CF_3. It is also preferred for R_1 and R_2, R_2 and R_3, R_3 and R_4 or R_4 and R_5 to form, together with the carbon atoms to which they are attached, a benzene ring.

Particularly preferred compounds are those wherein R_6, R_7, R_9 and R_{10} are each H, R_8 is selected from H, OMe and -NHAc and each of R_1 to R_5 is as specified above. In these preferred compounds R^1 to R^5 are preferably each independently selected from H, halogen, hydroxy, C_1-C_6 alkoxy, nitro, $-CH_2SCOR^{11}$, $-CH_2SR^{11}$, $-CO_2R^{11}$, $-OCOR^{13}$, CF_3, $-O(CH_2)_nN(R^{11}R^{12})$,$-O(CH_2)_nCO_2R^{11}$, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOR^{11}$, $-N(R^{11}R^{12})$,$-NHCO(CH_2)_nOCOR^{11}$, $-NHCO(CH_2)_nCO_2R^{11}$ and $-CH_2NHCO_2R^{13}$ or R_1 and R_2, R_2 and R_3, R_3 and R_4, or R_4 and R_5, form with the carbon atoms to which they are attached an optionally substituted benzene ring. Still more preferably, R_1 and R_2 are independently H, nitro or halogen, R_3 is H, hydroxy, $-O(CH_2)_nN(R^{11}R^{12})$,$-OCOR^{11}$, $-O(CH_2)_nCO_2R^{11}$, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, C_1-C_6 alkoxy, $-NHCO(CH_2)nOR^{11}$, $-NHCO(CH_2)_nOCOR^{11}$, $-N(R^{11}R^{12})$, $-CH_2NHCO_2R^{13}$, $-CH_2SR^{11}$ or $-NHCOR^{11}$; R_4 is H, halogen, C_1-C_6 alkoxy, $-CH_2SCOR^{11}$, $-CH_2SR^{11}$ or $-CO_2R^{11}$; and R_5 is H, nitro or halogen; or R_2 and R_3, R_3 and R_4 or R_4 and R_5 form, together with the carbon atoms to which they are attached, an optionally substituted benzene ring.

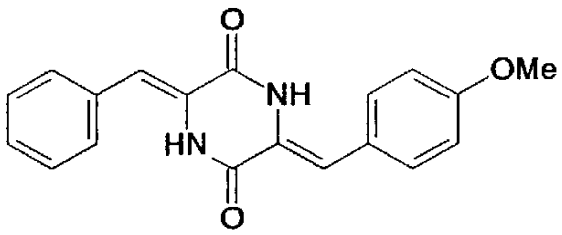
In one embodiment R_8 is NHAc, each of R_6, R_7, R_9 and R_{10} is H; R_1 is H or halogen such as Cl or F; R_2 is H, R_3 is halogen such as F or Cl, C_1-C_6 alkoxy such as OMe, $-N(R^{11}R^{12})$ such as NMe_2 or $-NHCOOR^{13}$ such as $-NHCOOBu^t$; R_4 is H and R_5 is halogen such as F, Cl, Br, or is CF_3.

In a second embodiment R_8 is OMe, each of R_6, R_7, R_9 and R_{10} is H; R^1 is H, nitro or halogen such as Cl; R^2 is H; R_3 is H, hydroxy, $-OCOR^{11}$ such as OAc, $-NHCO(CH_2)_nOCOR^{11}$ such as $-NHCOCH_2OAC$ or $-NHCOCH_2OR^{11}$ such

as -NHCOCH$_2$OH; R_4 is H and R_5 is H or halogen such as F or Cl; or R_2 and R_3 form a benzene ring together with the carbon atoms to which they are attached.

In a third embodiment each of R_1, R_6, R_7, R_8, R_9 and R_{10} is H; R_2 is H and R_3 is -CH$_2$SR^{11} such as -CH$_2$SMe, -CH$_2$SCOR^{11} such as -CH$_2$SAc, -NHCO(CH$_2$)$_n$CO$_2$R^{11} such as -NHCO(CH$_2$)$_3$CO$_2$Me, -O(CH$_2$)$_n$CO$_2$R^{11} such as -O(CH$_2$)$_4$CO$_2$H, -O(CH$_2$)N(R^{11}R^{12}) such as -O(CH$_2$)$_3$-NMe$_2$, or -N(R^{11}R^{12}) such as -NMe$_2$ or R_2 is -CH$_2$SCOR^{13} such as -CH$_2$SAc or -CH$_2$SR^{11} such as -CH$_2$SH and R_3 is H; and R_4 and R_5 are both H or both form, together with the carbon atoms to which they are attached, a benzene ring.

In one embodiment of the invention the compound of formula A is the following compound 3:



Certain diketopiperazines have been disclosed as having utility as bioactive agents. Yokoi et al in J.Antibiotics vol XLI No. 4, pp 494-501 (1988) describe structure-cytotoxicity relationship studies on a series of diketopiperazines related to neihumicin, a compound obtained from the micro-organism Micromonospora neihuensis. These are compounds of the above formula (A) wherein rings a and b, which are the same, are unsubstituted or substituted by chloro, methyl or methoxy groups. Kamei et at in J.Antibiotics vol XLIII No.8 1018-1020 disclose that two diketopiperazines, designated piperafizines A and B, have utility as potentiators of the cytotoxicity of vincristine. In J. Med. Chem 7(6) 821, (1964) and Chem. Abs. vol 62, n° 2775f (1964), Bahner et al describe the activity of 3,6-bis(p-dimethylaminobenzylidene)-2,5-dioxopiperazine in a tumour screening test.

Other compounds of the above formula (A) have been described in the literature with no indication that they are biologically active. Chem. Abs. vol. 117 n° 28 (1992) 90238v and Chem. Abs. vol. 65 N° 16969 a-f (1966) describe two series of such compounds wherein rings a and b, which are the same, are unsubstituted or substituted by halogen, nitro, methoxy, acetoxy, nitro or cyano groups.

Tetrahedron vol. 30 pp 667-673 (1974) describes such compounds wherein one or both of rings a and b is substituted by 4-nitro. Aust. J.Chem 1984, 37, 1791-4 discloses compounds of formula (I) wherein rings a and b are the same and are unsubstituted or substituted by 2 chloro or 4-acetoxy.

Each of the following references discloses a compound of formula (A) wherein rings a and b are the same and bear the substituents indicated:

Tetrahedron 47 n°30 (1991) 5643-5663, 2,4,5-trimethoxy-3-methyl;
Chem. Abs. vol 98 n° 28 (1983) 160674z, 2-carboxy; Chem. Abs. vol 97 n°6 (1982) 40323s, 4-amino; GB-A-917435, 3-carboxy-4-hydroxy; DE-B-621862, 2-fluoro; and Chem. Abs. Vol 62 n° 27758 (1964), 4-dimethylamino.
Bull. Chem. Soc. Japan 59, 3917-3923 (1986) and

Heterocycles vol 16 n° 9 1981 (1573-1578) each disclose a compound of formula (A) in which one of rings a and b is unsubstituted and the other is substituted by 2-hydroxy or 4-methoxy, respectively.

General formula A embraces diketopiperazines which are novel. Accordingly, the present invention provides a diketopiperazine of formula (A) as defined above, or a pharmaceutically acceptable salt or ester thereof; with the exception of compounds wherein:

(i) each of rings a and b, which are the same, is unsubstituted or substituted exclusively by 2-chloro, 3-chloro, 4-methyl, 4-acetoxy, 2-carboxy, 4-nitro, 4-amino, 2-bromo, 2-nitro, 4-chloro, 4-methoxy, 4-fluoro, 2-fluoro, 2-acetoxy, 3-nitro, 4-iodo, 4-cyano or 4-dimethylamino;
(ii) each of rings a and b, which are the same, is substituted exclusively by 2,5-dimethyl, 2,5-diacetoxy, 3,4-dimethoxy, 3,4,5-trimethoxy, 2,4,5-trimethoxy, 2,4,5-trimethoxy-3-methyl or 3-carboxy-4-hydroxy; and
(iii) one of rings a and b is unsubstituted and the other is substituted exclusively by 4-nitro, 4-methoxy or 2-hydroxy.

The present invention further provides a diketopiperazine of formula (A) as defined above wherein ring a bears a

different substitution pattern from ring b, or a pharmaceutically acceptable salt or ester thereof; with the exception of compounds wherein one of rings a and b is unsubstituted and the other is substituted exclusively by 4-nitro, 4-methoxy or 2-hydroxy.

The present invention further provides a compound for use as an inhibitor of plasminogen activator inhibitor, which compound is a diketopiperazine of formula (A) as defined above, or a pharmaceutically acceptable salt or ester thereof; with the exception of compounds wherein

(i) each of rings a and b, which are the same, is unsubstituted or substituted exclusively by 2-chloro, 3-chloro, 4-methyl or 4-dimethylamino; and

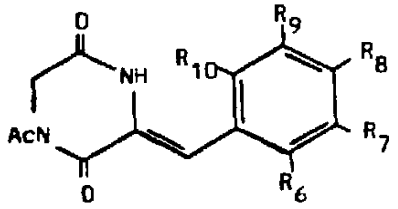
(ii) each of rings a and b, which are the same, is substituted exclusively by 2,5-dimethyl, 2,4,5-trimethoxy or 3,4,5-trimethoxy.

Examples of specific compounds of formula A are as follows. The compound numbering is adhered to in the rest of the specification:

(3Z,6Z,)-6-benylidene-3-(4-methoxybenzylidene)-2,5-piperazinedione (compound 3)
(3Z,6Z)-6-Benzylidene-3-(2,6-dichlorobenzylidene)-2,5-piperazinedione (compound 21)
(3Z,6Z)-3-(4-Acetoxybenzylidene) -6-benzylidene-2,5-piperazinedione (compound 23)
(3Z,6Z)-6-Benzylidene-3-(4-nitrobenzylidene)-2,5-piperazinedione (compound 74)
3,6-Dibenzylidene-2,5-piperazinedione (compound 22) (mixture of isomers)
(3Z,6Z)-6-Benzylidene-3-(3-nitrobenzylidene)-2,5-piperazinedione (compound 24)
(3Z,6Z)-6-Benzylidene-3-(2-nitrobenzylidene)-2,5-piperazinedione (compound 65)
(3Z,6Z)-6-Benzylidene-3-(4-ethoxybenzylidene)-2,5-piperazinedione (compound 25)
(3Z,6Z)-6-Benzylidene-3-(4-cyanobenzylidene)-2,5piperazinedione (compound 105)
(3Z,6Z)-3-(4-Aminobenzylidene) -6-benzylidene-2,5-piperazinedione (compound 30)
(3Z,6Z)-3-(3-Acetoxybenzylidene) -6-benzylidene-2,5-piperazinedione (compound 31)
(3Z,6Z)-3-(2-Acetoxybenzylidene) -6-benzylidene-2,5-piperazinedione (compound 32)
(3Z,6Z)-6-Benzylidene-3-(3-hydroxybenzylidene) -2,5-piperazinedione (compound 33)
(3Z,6Z)-3-(4-Acetamidobenzylidene) -6-benzylidene-2,5-piperazinedione (compound 34)
(3Z,6Z)-3-(2-Acetamidobenzylidene) -6-benzylidene-2,5-piperazinedione (compound 38)
(3Z,6Z)-3-(2-Aminobenzylidene)-6-benzylidene-2,5-piperazinedione (compound 39)
(3Z,6Z)-3-(4-Acetoxymethylbenzylidene) -6-benzylidene-2,5-piperazinedione (compound 43)
(3Z,6Z)-3-(4-Acetamidomethylbenzylidene)-6-benzylidene-2,5-piperazinedione (compound 44)
(3Z,6Z)-3,6-Dibenzylidene-2,5-piperazinedione (compound 45)
(3Z,6Z)-6-Benzylidene-3-(4-butoxybenzylidene)-2,5-piperazinedione (compound 48)
(3Z,6Z)-6-Benzylidene-3-(4-tert-butylbenzylidene)-2,5-piperazinedione (compound 51)
(3Z, 6Z)-6-Benzylidene-3-(4-isopropoxybenzylidene)-2,5-piperazinedione (compound 52)
(3Z,6Z)-6-Benzylidene-3-(2,4-difluorobenzylidene)-2,5-piperazinedione (compound 54)
(3Z,6Z)-6-Benzylidene-3-(2-bromobenzylidene)-2,5-piperazinedione (compound 55)
(3Z,6Z)-6-Benzylidene-3-(4-methylthiomethylbenzylidene)-2,5-piperazinedione (compound 59)
(3Z,6Z)-6-Benzylidene-3-(3-thioacetoxymethylbenzylidene)-2,5-piperazinedione (compound 61)
3-((3Z,6Z)-6-Benzylidene-2,5-dioxopiperazin-3-ylidene)methylbenzoic acid, methyl ester (compound 62)
(3Z,6Z)-6-Benzylidene-3-(3-mercaptomethylbenzylidene)-2,5-piperazinedione (compound 64)
(3Z,6Z)-6-Benzylidene-3-(4-tert-butoxycarbonylaminobenzylidene)-2,5-piperazinedione (compound 66)
(3Z,6Z)-6-Benzylidene-3-(4-(3-N,N-dimethylaminopropOxy) benzylidene)-2,5-piperazinedione (compound 75)
(3Z,6Z)-6-Benzylidene-3-(4-thioacetoxymethylbenzylidene)-2,5-piperazinedione (compound 76)
(3Z,6Z)-6-Benzylidene-3-(2-chloro-4-hydroxybenzylidene)-2,5-piperazinedione (compound 85)
(3Z,6Z)-6-Benzylidene-3-(3,4-dimethoxybenzylidene)-2,5-piperazinedione (compound 90)
4-[(3Z,6Z)-6-Benzylidene-2,5-dioxopiperazin-3-ylidene]methylphenoxyacetic acid, methyl ester (compound 93)
4-(4-[(3Z,6Z)-6-Benzylidene-2,5-dioxopiperazin-3-ylidene]methylbenzylcarbamoyl) butanoic acid, methyl ester (compound 94)
4-(4-((3Z,6Z)-6-Benzylidene-2,5-dioxopiperazin-3-ylidene)methylbenzylcarbamoyl)pentanoic acid, methyl ester (compound 95)
5-[4-((3Z,6Z)-6-Benzylidene-2,5-dioxopiperazin-3-ylidene)methylphenoxy]pentanoic acid, methyl ester (compound 96)
5-[4-((3Z,6Z)-6-Benzylidene-2,5-dioxopiperazin-3-ylidene)methylphenoxy]pentanoic acid (compound 97)
(3Z,6Z)-6-Benzylidene-3-(4-(2-N,N-dimethylaminoethoxy)benzylidene)-2,5-piperazinedione, hydrochloride (compound 99)

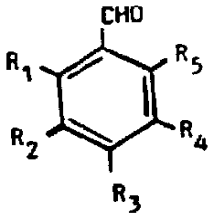
(3Z,6Z)-6-Benzylidene-3-(4-(2-N,N-dimethylaminoethoxy)benzylidene)-2,5-piperazinedione (compound 102)
4-[(3Z,6Z)-6-Benzylidene-2,5-dioxopiperazin-3-ylidene]methylphenoxyacetic acid (compound 101)
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione (compound 26)
(3Z,6Z)-6-(4-Methoxybenzylidene)-3-(2-nitrobenzylidene)-2,5-piperazinedione (compound 28)
(3Z,6Z)-3-(2,6-Dichlorobenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione (compound 29)
(3Z,6Z)-3-(4-Hydroxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione (compound 36)
(3Z,6Z)-3-(4-Acetoxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione (compound 37)
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(4-N-methylacetamidobenzylidene)-2,5-piperazinedione (compound 41)
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(4-methylsulfonylbenzylidene)-2,5-piperazinedione (compound 46)
(3Z,6Z)-3-(4-Butoxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione (compound 47)
(3Z,6Z)-3-(4-Isopropoxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione (compound 49)
(3Z,6Z)-3-(4-methoxybenzylidene)-6-(4-tert-butylbenzylidene)-2,5-piperazinedione (compound 50)
(3Z,6Z)-3-(2-Bromobenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione (compound 53)
(3Z,6Z)-(4-Methoxybenzylidene)-6-(4-tert-butoxycarbonylaminomethylbenzylidene)-2,5-piperazinedione (compound 56)
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(4-methylthiomethylbenzylidene)-2,5-piperazinedione (compound 57)
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(4-methylsulfonylmethylbenzylidene)-2,5-piperazinedione (compound 60)
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(3-thioacetoxymethylbenzylidene)-2,5-piperazinedione (compound 63)
(3Z,6Z)-3-(4-Aminomethylbenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione (compound 67)
(3Z,6Z)-3-(2,4-Difluorobenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione (compound 69)
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(2-trifluoromethylbenzylidene)-2,5-piperazinedione (compound 70)
(3Z,6Z)-3-(2,4-Dimethoxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione (compound 73)
4-[(3Z,62)-6-(4-Methoxybenzylidene)-2,5-dioxopiperazin-3-ylidene]methylbenzamide (compound 80)
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(4-trimethylacetoxybenzylidene)-2,5-piperazinedione (compound 81)
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(4-methoxycarbonylaminobenzylidene)-2,5-piperazinedione (compound 83)
(3Z,6Z)-3-(2-Chloro-4-hydroxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione (compound 84)
(3Z,6Z)-3-(4-Acetoxyacetylaminobenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione (compound 87)
(3Z,6Z)-3-(3,4-Dimethoxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione (compound 91)
4-((3Z,6Z)-6-(4-Methoxybenzylidene)-2,5-dioxopiperazin-3-ylidene)-4-methylbenzylcarbamoyl)butanoic acid, methyl ester (compound 100)
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(2-naphthylmethylene)-2,5-piperazinedione (compound 27)
(3Z,6Z)-3-(4-Hydroxyacetylaminobenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione (compound 88)
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-benzylidene-2,5-piperazinedione (compound 34)
(3Z,6Z)-3,6-Di-(3-Nitrobenzylidene)-2,5-piperazinedione (compound 35)
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(2,6-dichlorobenzylidene)-2,5-piperazinedione (compound 40)
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-chlorobenzylidene)-2,5-piperazinedione (compound 42)
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-acetoxymethylbenzylidene)-2,5-piperazinedione (compound 58)
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(2-fluorobenzylidene)-2,5-piperazinedione (compound 71)
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-fluorobenzylidene)-2,5-piperazinedione (compound 72)
(3Z,6Z)-6-(Benzylidene)-3-(2,4-difluorobenzylidene)-2,5-piperazinedione (compound 76)
(3Z,6Z)-6-(4-Acetamidobenzylidene)-3-(2-trifluoromethylbenzylidene)-2,5-piperazinedione (compound 78)
(3Z,6Z)-6-(4-Acetamidobenzylidene)-3-(2-bromobenzylidene)-2,5-piperazinedione (compound 79)
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-trimethylacetoxybenzylidene)-2,5-piperazinedione (compound 82)
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-dimethylaminobenzylidene)-2,5-piperazinedione (compound 86)
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-tert-butoxycarbonylaminomethylbenzylidene)-2,5-piperazinedione (compound 68)

Compounds of formula A, both known and novel, may be prepared by a process which comprises either (i) condensing compound of formula (I)



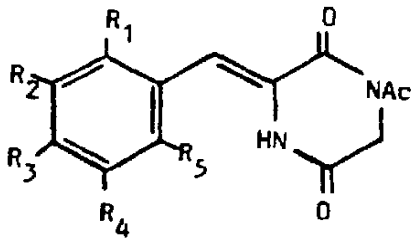
(I)

wherein R_6 to R_{10} are as defined above and are optionally protected, with a compound of formula (II):



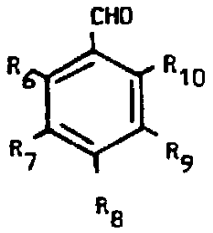
(II)

wherein R_1 to R_5 are defined above and are optionally protected, in the presence of a base in an organic solvent; or (ii) condensing a compound of formula (I'):



(I')

wherein R_1 to R_5 are as defined above and are optionally protected, with a compound of formula (III):



(III)

wherein R_6 to R_{10} are as defined above and are optionally protected, in the presence of a base in an organic solvent; and, in either case (i) or (ii), if required, removing optionally present protecting groups and/or, if desired, converting one compound of formula A into another compound of formula A, and/or, if desired, converting a compound of formula A into a pharmaceutically acceptable salt or ester thereof, and/or, if desired, converting a salt or ester into a free compound, and/or, if desired, separating a mixture of isomers of compounds of formula A into the single isomers.

A compound of formula A produced directly by the condensation reaction between (I) and (II) or (I') and (III) may be modified, if desired, by converting one or more of groups R_1 to R_{10} into different groups R_1 to R_{10}. These optional conversions may be carried out by methods known in themselves. For example, a compound of formula A in which one or more of R_1 to R_{10} is an ester group may be converted to a compound of formula A wherein the corresponding substituent is a free -COOH group, by acid or alkaline hydrolysis at a suitable temperature, for example from ambient temperature to 100°C.

A compound of formula A in which one or more of R_1 to R_{10} is a $-CO_2H$ group may be converted into a compound of formula A wherein the corresponding substituent is esterified by esterification, for example by treating the carboxylic acid with a suitable C_1-C_6 alkyl alcohol in the presence of 1,3-dicyclohexylcarbodiimide in an inert solvent.

A compound of formula A in which one or more of R_1 to R_{10} is a free $-CO_2H$ group may be converted into a compound of formula A in which the corresponding substituent is a group $-CON(R^{11}R^{12})$, wherein R^{11} and R^{12} are as defined above, for example by treatment with ammonia or an amine in the presence of I,3-dicyclohexylcarbodiimide in an inert solvent.

A compound of formula A in which one or more of R_1 to R_{10} is a free $-CO_2H$ group may be converted into a compound of formula A wherein the corresponding substituent is a $-CH_2OH$ group by reduction, for example using borane in a suitable solvent such as tetrahydrofuran.

A compound of formula A in which one or more of R_1 to R_{10} is a nitro group may be converted into a compound of formula A in which the corresponding substituent is an amino group by reduction under standard conditions, for

example by catalytic hydrogenation.

Protecting groups for R_1 to R_{10} in any of the compounds of formulae (I), (I'), (II) and (III) are optionally introduced prior to step (i) or step (ii) when any of groups R_1 to R_{10} are groups which are sensitive to the condensation reaction conditions or incompatible with the condensation reaction, for example a -COOH, $-CH_2OH$ or amino group. The protecting groups are then removed at the end of the process. Any conventional protecting group suitable for the group R_1 to R_{10} in question may be employed, and may be introduced and subsequently removed by well-known standard methods.

The condensation reaction between compounds (I) and (II) or (I') and (III) is suitably performed in the presence of a base which is potassium t-butoxide, sodium hydride, potassium carbonate, sodium carbonate, caesium carbonate, sodium acetate, potassium fluoride on alumina, or triethylamine in a solvent such as dimethylformamide, or in the presence of potassium t-butoxide in t-butanol or a mixture of t-butanol and dimethylformamide. The reaction is typically performed at a temperature from 0°C to the reflux temperature of the solvent.

The compounds of formula (I) may be prepared by a process comprising reacting 1,4-diacetyl-2,5-piperazinedione with a compound of formula (III) as defined above, in the presence of a base in an organic solvent. Similarly, the compounds of formula (I') may be prepared by a process which comprises reacting 1,4-diacetyl-2,5-piperazinedione with a compound of formula (II) as defined above, in the presence of a base in an organic solvent.

If necessary, the resulting compound of formula (I) or (I') can be separated from other reaction products by chromatography.

The reaction of 1,4-diacetyl-2,5-piperazinedione with the compound of formula (III) or (II) is suitably performed under the same conditions as described above for the condensation between compounds (I) and (II), or (I') and (III).

The substituted benzaldehydes of formulae (II) and (III) are known compounds or can be prepared from readily available starting materials by conventional methods. The l,4-diacetyl-2,5-piperazinedione used as a starting material in the preparation of compounds of formula (I) may be prepared by treating 2,5-piperazinedione (glycine anhydride) with an acetylating agent. The acetylation may be performed using any conventional acetylating agent, for example acetic anhydride under reflux or, alternatively, acetic anhydride at a temperature below reflux in the presence of 4-dimethylaminopyridine.

Compounds of formula (I) may also be prepared by the microwave irradiation of a mixture comprising 1,4-diacetyl-2,5-piperazinedione, a compound of formula (III) and potassium fluoride on alumina (as base) in the absence of solvent.

Compounds of formula (I) may alternatively be prepared directly from 2,5-piperazinedione (glycine anhydride) by a process which comprises treating the 2,5-piperazinedione with a mixture comprising a compound of formula (III), sodium acetate and acetic anhydride at an elevated temperature, for example under reflux.

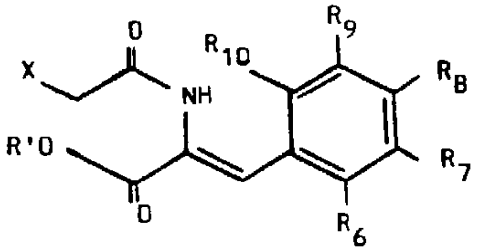
Compounds of formula (I') may be prepared by analogous processes, replacing compound (III) in each case by a compound of formula (II).

Compounds of formula A may also be prepared by a process comprising the microwave irradiation of (i) a mixture comprising a compound of formula (I) as defined above, a compound of formula (II) and potassium fluoride on alumina, or (ii) a mixture comprising a compound of formula (I') a compound of formula (III) and potassium fluoride on alumina, or (iii) a mixture comprising 1,4-diacetyl-2,5-piperazinedione, a compound of formula (II), a compound of formula (III) and potassium fluoride on alumina. The irradiation is performed in the absence of a solvent.

Compounds of formula (A) may also be obtained directly by a process which comprises condensing together l, 4-diacetyl-2,5-piperazinedione, a compound of formula (II) and a compound of formula (III) in the presence of a base in an organic solvent. Suitable bases, solvents and reaction conditions are as described above for the condensation reaction between, for example, compounds (I) and (II).

An alternative direct process for the preparation of compounds of formula (A) comprises condensing together 2,5-piperazinedione, a compound of formula (II) and a compound of formula (III) in the presence of sodium acetate and acetic anhydride at elevated temperature, for example under reflux.

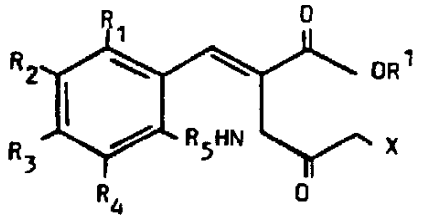
An alternative process for the preparation of compounds of formula (I) comprises treating a compound of formula (V):



(V)

wherein R_6 to R_{10} are as defined above, X is a halogen and R' is a C_1-C_6 alkyl group, with ammonia followed by acetic anhydride.

Compounds of formula (I') may be prepared by an analogous process which comprises treating a compound of formula (V'):



(V')

wherein R_1 to R_5, X and R^1 are as defined above, with ammonia followed by acetic anhydride.

X in formula (V) or (V') is typically iodine. R^1 is, for example, a C_1-C_4 alkyl group such as a methyl, ethyl, propyl, i-propyl, butyl, sec-butyl or tert-butyl group.

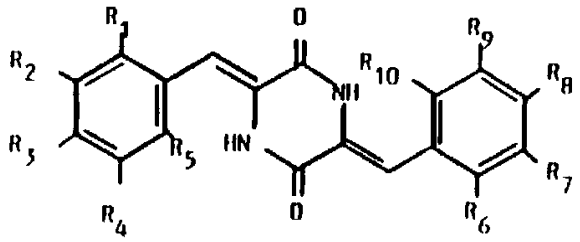
A review of synthetic approaches to unsaturated 3-monosubstituted and 3,6-disubstituted-2,5-piperazinediones is provided in Heterocycles, 1983, 20, 1407 (C.Shin).

Compounds of formula (A) may be converted into pharmaceutically acceptable salts, and salts may be converted into the free compound, by conventional methods. Suitable salts include salts with pharmaceutically acceptable, inorganic or organic, bases. Examples of inorganic bases include ammonia and carbonates, hydroxides and hydrogen carbonates of group I and group II metals such as sodium, potassium, magnesium and calcium. Examples of organic bases include aliphatic and aromatic amines such as methylamine, triethylamine, benzylamine, dibenzylamine or α- or β-phenylethylamine, and heterocyclic bases such as piperidine, 1-methylpiperidine and morpholine.

Compounds of formula (A) may also be converted into pharmaceutically acceptable esters. Suitable esters include branched or unbranched, saturated or unsaturated C_1-C_6 alkyl esters, for example methyl, ethyl and vinyl esters.

Preferred compounds of formula A are depicted by means of their subsitution patterns in Table 1 which follows. The compound numbering is adhered to in the rest of the specification. Characterising data for the compounds are set out in Table 2 in Example 16.

TABLE 1



COMPOUND NO.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	PREPARED IN EXAMPLE
21	Cl	H	H	H	Cl	H	H	H	H	H	5
22	H	H	H	H	H	H	H	H	H	H	10
23	H	H	OAc	H	H	H	H	H	H	H	6
24	H	NO_2	H	H	H	H	H	H	H	H	6
25	H	H	OEt	H	H	H	H	H	H	H	5
26	H	H	NHAc	H	H	H	H	OMe	H	H	7
27	H	- Benzene -		H	H	H	H	OMe	H	H	14
28	NO_2	H	H	H	H	H	H	OMe	H	H	8
29	Cl	H	H	H	Cl	H	H	OMe	H	H	7
30	H	H	NH_2	H	H	H	H	H	H	H	13
31	H	OAc	H	H	H	H	H	H	H	H	6
32	OAc	H	H	H	H	H	H	H	H	H	6

COMPOUND NO.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	PREPARED IN EXAMPLE
33	H	OH	H	H	H	H	H	H	H	H	13
34	H	H	NHAc	H	H	H	H	H	H	H	5
35	H	NO_2	H	H	H	H	NO_2	H	H	H	11
36	H	H	OH	H	H	H	H	OMe	H	H	13
37	H	H	OAc	H	H	H	H	OMe	H	H	7
38	NHAc	H	H	H	H	H	H	H	H	H	5
39	NH_2	H	H	H	H	H	H	H	H	H	13
40	H	H	NHAc	H	H	Cl	H	H	H	Cl	9
41	H	H	NMeAc	H	H	H	H	OMe	H	H	7
42	H	H	Cl	H	H	H	H	NHAc	H	H	9
43	H	H	CH_2OAc	H	H	H	H	H	H	H	5
44	H	H	CH_2NHAc	H	H	H	H	H	H	H	5
45	H	H	H	H	H	H	H	H	H	H	5
46	H	H	SO_2Me	H	H	H	H	OMe	H	H	7
47	H	H	OBu^n	H	H	H	H	OMe	H	H	7
48	H	H	OBu^n	H	H	H	H	H	H	H	5
49	H	H	OPr^i	H	H	H	H	OMe	H	H	7
50	H	H	Bu^t	H	H	H	H	OMe	H	H	7
51	H	H	Bu^t	H	H	H	H	H	H	H	5

COMPOUND NO.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	PREPARED IN EXAMPLE
52	H	H	OPr^i	H	H	H	H	H	H	H	5
53	Br	H	H	H	H	H	H	OMe	H	H	7
54	F	H	F	H	H	H	H	H	H	H	5
55	Br	H	H	H	H	H	H	H	H	H	5
56	H	H	CH_2NHBOC	H	H	H	H	OMe	H	H	7
57	H	H	OMe	H	H	H	H	CH_2SMe	H	H	7
58	H	H	NHAc	H	H	H	H	CH_2OAc	H	H	9
59	H	H	H	H	H	H	H	CH_2SMe	H	H	5
60	H	H	OMe	H	H	H	H	CH_2SO_2Me	H	H	7
61	H	CH_2SAc	H	H	H	H	H	H	H	H	5
62	H	CO_2Me	H	H	H	H	H	H	H	H	5
63	H	CH_2SAc	H	H	H	H	H	OMe	H	H	7
64	H	CH_2SH	H	H	H	H	H	H	H	H	13
65	NO_2	H	H	H	H	H	H	H	H	H	6
66	H	H	CH_2NHBOC	H	H	H	H	H	H	H	5
67	H	H	CH_2NH_2	H	H	H	H	OMe	H	H	13
68	H	H	CH_2NHBOC	H	H	H	H	NHAc	H	H	9
69	F	H	F	H	H	H	H	OMe	H	H	7
70	CF_3	H	H	H	H	H	H	OMe	H	H	7

COMPOUND NO.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	PREPARED IN EXAMPLE
71	F	H	H	H	H	H	H	NHAc	H	H	9
72	H	H	F	H	H	H	H	NHAc	H	H	9
73	OMe	H	OMe	H	H	H	H	OMe	H	H	7
74	H	H	NO_2	H	H	H	H	H	H	H	6
75	H	H	H	H	H	H	H	$O(CH_2)_3NMe_2$	H	H	5
76	H	H	H	H	H	H	H	CH_2SAc	H	H	5
77	F	H	F	H	H	H	H	NHAc	H	H	9
78	CF_3	H	H	H	H	H	H	NHAc	H	H	9
79	Br	H	H	H	H	H	H	NHAc	H	H	9
80	H	H	OMe	H	H	H	H	$CONH_2$	H	H	7
81	H	H	OMe	H	H	H	H	OCOBu^t	H	H	7
82	H	H	NHAc	H	H	H	H	OCOBu^t	H	H	9
83	H	H	NHCOOMe	H	H	H	H	OMe	H	H	7
84	Cl	H	OH	H	H	H	H	OMe	H	H	7
85	Cl	H	OH	H	H	H	H	H	H	H	5
86	H	H	NHAc	H	H	H	H	NMe_2	H	H	12
87	H	H	$NHCOCH_2OAc$	H	H	H	H	OMe	H	H	7
88	H	H	$NHCOCH_2OH$	H	H	H	H	OMe	H	H	13
89	H	H	H	H	H	-Benzene-		NMe_2	H	H	5

COMPOUND NO.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	R_{10}	PREPARED IN EXAMPLE
90	H	OMe	OMe	H	H	H	H	H	H	H	5
91	H	OMe	OMe	H	H	H	H	OMe	H	H	7
92	H	OMe	OMe	H	H	H	H	NHAc	H	H	9
93	H	H	OCH_2CO_2Me	H	H	H	H	H	H	H	5
94	H	H	$CH_2NHCO(CH_2)_3CO_2Me$	H	H	H	H	H	H	H	5
95	H	H	$CH_2NHCO(CH_2)_4CO_2Et$	H	H	H	H	H	H	H	5
96	H	H	$O(CH_2)_4CO_2Me$	H	H	H	H	H	H	H	5
97	H	H	$O(CH_2)_4CO_2H$	H	H	H	H	H	H	H	13
98	H	H	$O(CH_2)_3NMe_2.HCl$	H	H	H	H	H	H	H	15
99	H	H	$O(CH_2)_2NMe_2.HCl$	H	H	H	H	H	H	H	15
100	H	H	$CH_2NHCO(CH_2)_3CO_2Me$	H	H	H	H	OMe	H	H	7
101	H	H	OCH_2CO_2H	H	H	H	H	H	H	H	13
102	H	H	$O(CH_2)_2NMe_2$	H	H	H	H	H	H	H	5
103	F	H	H	H	H	H	H	OMe	H	H	7
104	H	H	CH_2OH	H	H	H	H	NHAc	H	H	13
105	H	H	H	H	H	H	H	CN	H	H	6

The diketopiperazines of formula (A), both novel and known and their pharmaceutically acceptable salts and esters (referred to hereinafter as the "present compounds") have utility as inhibitors of PAI. Elevated levels of PAI-1, by reducing the net endogenous fibrinolytic capacity, can contribute to the pathogenesis of various thrombotic disorders including myocardial infarction, deep vein thrombosis and disseminated intravascular coagulation. The present compounds therefore can act as inhibitors of the tPA/PAI-1 interaction. The present compounds can be used in the treatment of haemostatic disorders. A human or animal, e.g. a mammal, can therefore be treated by a method comprising administration of a therapeutically effective amount of a diketopiperazine of formula (A) or a pharmaceutically or veterinarily acceptable salt thereof.

Tissue plasminogen activator (tPA) is used as a fibrinolytic agent in the treatment of thrombotic disorders. The efficacy of the tPA in this role may be enhanced if it is administered together with a PAI inhibitor. A human or animal, e.g. a mammal, can therefore be treated by a method comprising the combined administration of a therapeutically effective amount of tPA and a therapeutically effective amount of any one of the present compounds. The present invention also provides products containing a diketopiperazine of formula (A) or a pharmaceutically acceptable salt or ester thereof and tPA as a combined preparation for simultaneous, separate or sequential use in the treatment of thrombotic disorders, for example where there is inappropriate PAI activity. In such products the present compound is formulated for oral or parenteral (intravenous, intramuscular or subcutaneous) administration and the tPA is formulated for intravenous administration.

As one example, during acute myocardial infarction (MI) one of the present compounds may be administered to a patient together with tPA to enhance the efficacy of the tPA treatment. As a further example, early re-occlusion following treatment of a patient with tPA may be prevented by the post-MI administration of one of the present compounds.

The compounds of formula (A) have been tested in a PAI functional assay. In this assay, a compound is incubated with PAI-1 prior to addition to the tPA assay system. Inhibition of PAI-1 results in the production of plasmin from plasminogen. In turn, plasmin cleaves the chromogenic substrate S2251 (Kabi Vitrum) producing pNA (p-nitroaniline) which is detected spectrophotometrically at 405 nm (K.Nilsson et al, Fibrinolysis (1987) 1, 163-168). The results of the assay are reported in Example 1 which follows.

The present compounds can be administered in a variety of dosage forms, for example orally such as in the form of tablets, capsules, sugar- or film-coated tablets, liquid solutions or suspensions or parenterally, for example intramuscularly, intravenously or subcutaneously. The present compounds may therefore be given by injection or infusion.

The dosage depends on a variety of factors including the age, weight and condition of the patient and the route of administration. Typically, however, the dosage adopted for each route of administration when a compound of the invention is administered alone to adult humans is 0.001 to 10 mg/kg, most commonly in the range of 0.01 to 5 mg/kg, body weight. Such a dosage may be given, for example, from 1 to 5 times daily by bolus infusion, infusion over several hours and/or repeated administration.

When one of the present compounds is administered in combination with tPA to adult humans, the dosage adopted for each route of administration is typically from 0.001 to 10 mg, more typically 0.01 to 5 mg per kg body weight for a compound of the invention and from 5 to 500mg administered intravenously for the tPA. A suitable dosage regimen for the tPA is 100 mg given intravenously over 3 hours as follows: 10% of the total dose as an i.v. bolus over 1-2 minutes, 50% of the total dose as an infusion over 1 hour, 40% of the total dose as an infusion over the subsequent 2 hours.

The present invention further provides a pharmaceutical or veterinary composition comprising a pharmaceutically or veterinary acceptable carrier or diluent and, as an active principle, a compound which is a diketopiperazine of formula (A) as defined above or a pharmaceutically acceptable salt or ester thereof; with the exception of compounds wherein:

(i) each of rings a and b, which are the same, is unsubstituted or substituted exclusively by 2-chloro, 3-chloro, 4-methyl or 4-dimethylamino; and
(ii) each of rings a and b, which are the same, is substituted exclusively by 2,5-dimethyl, 2,4,5-trimethoxy or 3,4,5-trimethoxy.

For example, the solid oral forms may contain, together with the active compound, diluents such as lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants such as silica, talc, stearic acid, magnesium or calcium stearate and/or polyethylene glycols; binding agents such as starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose, or polyvinyl pyrrolidone; disintegrating agents such as starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs, sweeteners; wetting agents such as lecithin, polysorbates, lauryl sulphates. Such preparations may be manufactured in known manners, for example by means of mixing, granulating, tabletting, sugar coating, or film-coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carrier, for example, saccharose or saccharose with glycerol and/or mannitol and/or sorbitol. In particular, a syrup for

diabetic patients can contain as carriers only products, for example sorbitol, which do not metabolise to glucose or which only metabolise a very small amount to glucose. The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose or polyvinyl alcohol.

Suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier such as sterile water, olive oil, ethyl oleate, glycols such as propylene glycol, and, if desired, a suitable amount of lidocaine hydrochloride. Some of the present compounds are insoluble in water. A compound may be encapsulated within liposomes.

The following Examples illustrate the invention:

EXAMPLE 1 : TESTING OF THE PRESENT COMPOUNDS AS PAI INHIBITORS

Compounds of formula (A) were tested in a PAI chromogenic substrate assay. In the first assay (K.Nilsson, Fibrinolysis (1987) 1, 163-168) each compound was incubated with PAI-1 prior to addition to the tPA assay system. Inhibition of PAI-1 by the compound of formula (Aa) resulted in the production of plasmin from plasminogen. In turn, the plasmin cleaved the chromogenic substrate S2251 (Kabi-Vitrum) producing pNA (p-nitroaniline) which was detected spectrophotometrically at 405 nm.

The degrees of inhibition observed in the chromogenic substrate assay at various concentrations of compounds of formula (A) are presented in Table 3.

TABLE 3:

INHIBITION OF PAI-1 IN THE FIRST S225 CHROMOGENIC SUBSTRATE ASSAY					
Compound No.	**Concentration in μm**				
	100	**50**	**25**	**12.5**	**6.25**
21	79	35	2	0	0
22	61	2	1	0	0
25	52	25	1	0	0
27	70	35	8	9	
28	71	74	45	1	0
29	80	76	34	1	0
30	66	23	5	2	
31	58	12	2	1	0
32	87	36	3	1	0
33	56	3	1	1	0
35	52	28	2		
36	71	6	1		
37	69	19	2		
38	64	3	1	1	1
39	67	20	1	1	0
40	61	61	23	4	1
41	51	45	32	8	3
43	59	45	3	1	1
44	51	2	1	1	1
45	53	13	1	1	
46	39	42	38	14	
47	75	58	14	14	
48	73	57	26	3	

TABLE 3: (continued)

INHIBITION OF PAI-1 IN THE FIRST S225 CHROMOGENIC SUBSTRATE ASSAY					
Compound No.	Concentration in μm				
	100	50	25	12.5	6.25
49	60	47	8	1	
50	62	37	22	2	
51	79	61	38	5	
52	68	45	15	2	
53	56	32	9	2	
54	50	0	1	0	
55	65	43	11	1	
56	82	60	15	2	
57	82	72	38	2	
58	60	31	1	1	
59	71	76	60	19	
60	62	52	25	1	
61	83	88	69	26	
62	83	33	13	36	
63	69	70	44	36	
66	85	70	46	2	
67	53	60	46	2	
68	63	89	67	37	
69	68	40	14	3	
70	94	78	21	4	
73	50	3	1	2	
75	59	52	33	6	2
76	66	75	50	5	2
77	33	66	80	61	1
78	30	57	36	4	2
79	42	55	27	2	1
80	53	9	1	0	
81	64	1	1	0	
82	80	3	1	1	
83	56	1	1	1	
84	52	38	10	2	1
85	35	49	43	27	13
86	23	37	48	41	31
87	78	81	70	28	0
88	41	49	60	40	0
89	63	55	66	40	7

TABLE 3: (continued)

INHIBITION OF PAI-1 IN THE FIRST S225 CHROMOGENIC SUBSTRATE ASSAY					
Compound No.	**Concentration in μm**				
	100	**50**	**25**	**12.5**	**6.25**
90	75	58	33	6	0
91	50	72	3	0	0
92	86	44	38	12	17
93	71	68	39	7	2
94	31	62	83	76	43
95	69	71	45	16	10
96	77	75	47	29	5
97	0	24	73	0	0
98	72	71	74	67	4
Compound No.	**Concentration in μm**				
	60	**30**	**15**	**7.5**	**3.75**
23	65	17	0	0	
24	56	29	0	0	0
36	57	71	73	42	
34	72	77	76	24	
42	58	57	59	4	1
64	100	87	63	17	
71	52	64	51	1	1
72	76	75	18	1	1
Compound No.	**Concentration in μm**				
	40	**20**	**10**	**5**	**2.5**
99	68	48	17	0	0
Compound No.	**Concentration in μm**				
	100	**50**	**25**	**12**	**6**
3	86	74	53	40	14

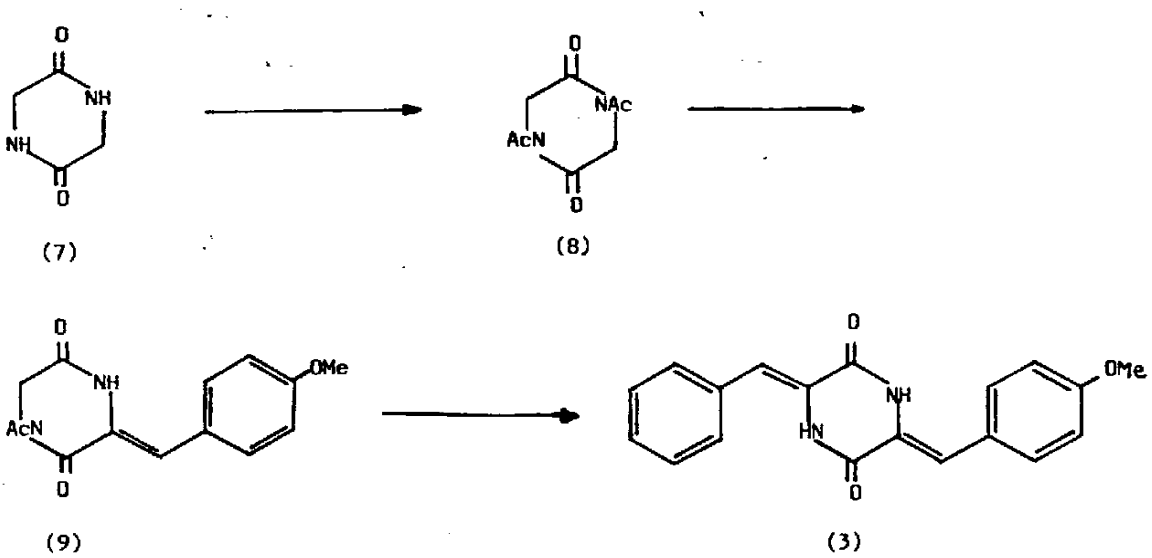
EXAMPLE 2 : PHARMACEUTICAL COMPOSITION

Tablets, each weighing 0.15 g and containing 25 mg of a compound of the invention can be manufactured as follows:
Composition for 10,000 tablets

compound of the invention (250 g)
lactose (800 g)
corn starch (415 g)
talc powder (30 g)
magnesium stearate (5 g)

The compound of the invention, lactose and half of the corn starch are mixed. The mixture is then forced through a sieve 0.5 mm mesh size. Corn starch (10 g) is suspended in warm water (90 ml). The resulting paste is used to granulate the powder. The granulate is dried and broken up into small fragments on a sieve of 1.4 mm mesh size. The remaining quantity of starch, talc and magnesium stearate is added, carefully mixed and processed into tablets.

REFERENCE EXAMPLE 1: PREPARATION OF (3Z,6Z)-3-BENZYLIDENE-6-(4-METHOXYBENZYLIDENE)-2,5-PIPERAZINEDIONE (3) (SCHEME 1)



1,4-Diacetyl-2,5-Piperazinedione (8)

1,4-Diacetyl-2,5-piperazine-2,5-dione (8) was prepared by the published procedure (S.M. Marcuccio and J.A. Elix, Aust. J. Chem., 1984, 37, 1791).

(3Z)-1-Acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (9)

(3Z)-1-Acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (9) was prepared by the published procedure (T. Yokoi, L-M. Yang, T. Yokoi, R-Y. Wu, and K-H. Lee, J. Antibiot., 1988, 41, 494).

(3Z,6Z)-3-Benzylidene-6-(4-methoxybenzylidene)-2,5-piperazinedione (3)

A mixture of (3Z)-1-acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (9) (1.0g, 3.6 mmol), benzaldehyde (430 µl, 4.2 mmol) and triethylamine (1.14 ml), 8.2 mmol), in dry DMF (20 ml), was heated at 130°C for 18h. The reaction mixture was cooled to room temperature and poured into ethyl acetate (100 ml). A yellow solid precipitated which was filtered off and dried. Yield 360 mg (31%).

$C_{19}H_{16}N_2O_3$

^1H nmr (400 MHz d_6-DMSO):

δ: 3.80 (3H, s, o-Me); 6.77 (1H, s, CH=C);
6.78 (1H, s, CH=C); 6.98 (2H, d, J=8Hz, 2xC-H on Ar-OMe); 7.30-7.56 (7H, m, Ph and 2xC-H on Ar-OMe);
10.15 (2H, br.s, N-H).

^{13}C nmr (100 MHz d_6-DMSO)

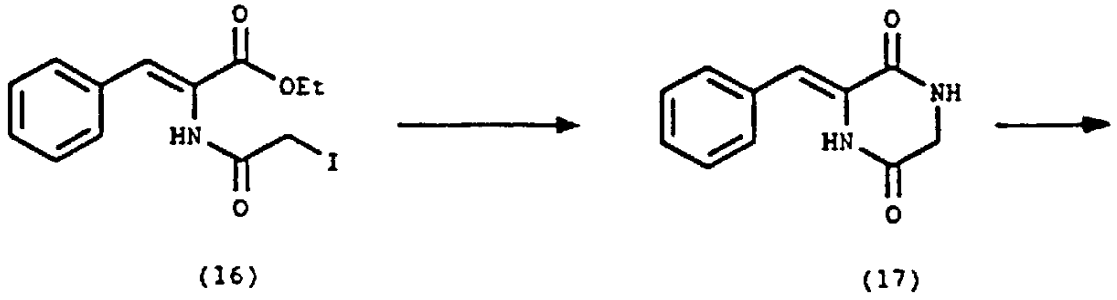
δ: 58.68; 117.66; 118.03; 118.77; 128.11; 128.92;
129.95; 131.53; 132.11; 132.69; 134.44; 136.59;
161.39; 161.62; 162.71.

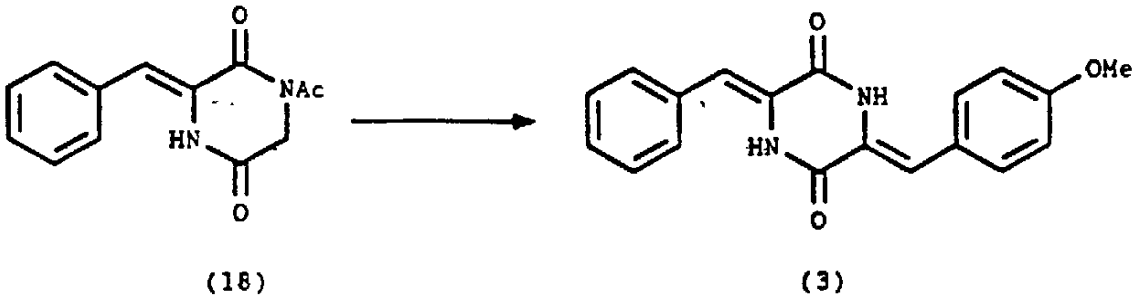
ms (desorption chemical ionisation, ammonia):
m/z (% relative intensity) : 321 (100) MH^+.
ir : KBr (diffuse reflectance):

v max (cm^{-1}) : 1620, 1700, 3100, 3220.

Elemental analysis:			
Calculated for $C_{19}H_{16}N_2O_3$:	C 71.24,	H 5.03,	N 8.74.
Found:	C 70.92,	H 5.02,	N 8.80.
	C 70.89,	H 5.06,	N 8.79%

REFERENCE EXAMPLE 2: PREPARATION OF (3Z,6Z)-3-BENZYLIDENE -6-(4-METHOXYBENZYLIDENE-1-METHYL-2,5-PIPERAZINEDIONE (3) (SCHEME 2)





Compound 16 is treated with ammonia and subsequently with acetic anhydride to yield 1-acetyl-3-benzylidenepiperazine-2,5-dione (18).

Compound 18 is then condensed, in the presence of caesium carbonate or triethylamine in DMF, with 4-methoxybenzaldehyde to yield compound 3.

Reference Example 3: Preparation of 1-acetyl-3-benzylidene-2,5-piperazinedione

1,4-Diacetyl-2,5-piperazinedione (25.0g, 126 mmol), which is compound (8) mentioned in Reference Example 1, was heated at 120-130°C in DMF (200 ml) with triethylamine (17.6 ml, 126 mmol) and benzaldehyde (13.0 ml, 126 mmol). After 4 h the mixture was cooled to room temperature and poured into EtOAc (1000 ml), and washed three times with brine. Any solid formed at this stage was filtered off. The filtrate was dried ($MgSO_4$) and the solvent removed in vacuo. The residue was recrystallised from EtOAc:Hexane to give 11.78 g (38%) of the title compound as a yellow solid.

^1H NMR ($CDCl_3$ 400 MHz) δ=2.69 (3H, s) 4.54 (2H, s) 7.20 (1H, s) 7.40 (3H, m), 7.48 (2H, m), 7.93 (1H, br.s)

MS(DCI,NH_3): 262 (MNH_4^+, 20%), 245 (MH^+, 53%), 220 (52%), 204 (100%), 203 (100%)

Microanalysis	C	H	N
Calc	63.93	4.95	11.47
Found	64.11	5.02	11.41
	64.05	4.90	11.44

Example 3: Preparation of compound 96

1-Acetyl-3-benzylidene-2,5-piperazinedione (one equivalent), prepared according to Reference Example 3, was treated with 5-(4-formylphenoxy)pentanoic acid, methyl ester in the presence of Cs_2CO_3 (1-1.1 equivalents) in DMF at 80-100°C for 1-8 hours. The title compound was obtained in 39% yield.

By the same method, but replacing 5-(4-formylphenoxy)pentanoic acid, methyl ester (which is benzaldehyde substituted at position 4 by $-O(CH_2)_4CO_2Me$) by the appropriately substituted benzaldehyde, the following compounds were prepared:

Compound	Yield (%)	Compound	Yield (%)
21	66	25	37
34	56	43	54
38	84	45	91
44	44	51	68
48	69	54	69

Characterising data for the compounds are set out in Example 14.

Example 4: Preparation of Compound 31

1-Acetyl-3-benzylidene-2,5-piperazinedione (one equivalent), prepared according to Reference Example 3, was treated with 3-acetoxybenzaldehyde (one equivalent) in the presence of triethylamine (1-2 equivalents) in DMF at 130°C for 2-6 hours. The title compound was obtained in 61% yield.

By the same method, but replacing 3-acetoxybenzaldehyde by the appropriately substituted benzaldehyde, the following compounds were prepared:

Compound	Yield (%)
23	16
24	43
32	41
65	27
74	77
105	50

Characterising data are provided in Example 14.

Example 5: Preparation of compound 103

1-Acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (1 equivalent), which is compound (9) mentioned in Reference Example 1, was treated with 2-fluorobenzaldehyde (1 equivalent) in the presence of Cs_2CO_3 (1-1.1 equivalents)

in DMF at 80-100°C for 1-6 hours. The title compound was obtained in 69% yield.

By the same method, but replacing the 2-fluorobenzaldehyde by the appropriately substituted benzaldehyde with the exception of compound 84 which was prepared by condensation with 4-acetoxy-2-chlorobenzaldehyde, the following compounds were prepared:

Compound	Yield (%)	Compound	Yield (%)
26	80	63	71
29	70	69	20
37	21	70	10
41	34	73	38
46	16	80	45
47	46	81	5
49	60	83	41
50	56	84	Low
53	77	87	33
57	49	91	74
60	71	100	20
		103	69

Characterising data are provided in Example 14.

Example 6: Preparation of compound 28

1-Acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (1 equivalent), compound (9) in Reference Example 1, was treated with 2-nitrobenzaldehyde (1 equivalent) in triethylamine (1-2 equivalents) and DMF at 130°C for 2-6 hours. The title compound was obtained in 45% yield. Characterising data are set out in Example 14.

Reference Example 4: Preparation of 1-acetyl-3-(4-acetamidobenzylidene)-2,5 -Piperazinedione

1,4-Diacetyl-2,5-piperazinedione (10.0g, 50 mmol), prepared by the published procedure mentioned in Reference Example 1, was stirred in DMF (40 ml) with 4-acetamidobenzaldehyde (8.24 g, 50 mmol) and triethylamine (7 ml, 50 mmol) and heated to 120°C. After 2½ h the mixture was cooled to room temperature, diluted with EtOAc (100 ml) and stirred overnight. The solid formed was collected, washed with EtOAc and dried to give 8.46 g (56%) of a yellow solid.

^{1}H NMR ($CDCl_3$+TFA, 400 MHz) δ=2.32 (3H, s) 2.72 (3H, s) 4.68 (2H, s) 7.36 (1H, s) 7.45 (2H, d, J=8Hz) 7.60 (2H, d, J=8Hz)

Microanalysis	C	H	N
Calc	59.80	5.02	13.95
Found	60.08	5.09	13.89
	60.11	5.07	13.86

Example 7: Preparation of Compound 77

1-Acetyl-3-(4-acetamidobenzylidene)-2,5-piperazinedione (1 equivalent), prepared according to Reference Exam-

ple 4, was treated with 2,4-difluorobenzaldehyde (1 equivalent) in the presence of Cs_2CO_3 (1-1.1 equivalents) in DMF at 80-100°C for 1-6 hours. The title compound was obtained in 60% yield.

By the same method, but replacing 2,4-difluorobenzaldehyde by the appropriately substituted benzaldehyde, the following compounds were obtained:

Compound	Yield (%)	Compound	Yield (%)
42	50	40	40
68	26	58	22
72	41	71	36

Characterising data are set out in Example 16.

Example 8: Preparation of compound 22

1,4-Diacetyl-2,5-piperazinedione (1 equivalent), prepared by the published procedure mentioned in Reference Example 1, was treated with benzaldehyde (2.1 equivalents) in the presence of triethylamine (2.5 equivalents) in DMF at 130°C for 8 hours. The title compound was obtained in 89% yield. Characterising data are set out in Example 14.

Example 9: Preparation of compound 35

1,4-Diacetyl-2,5-piperazinedione (1 equivalent), prepared by the published procedure mentioned in Example 3, was treated with 3-nitrobenzaldehyde (1 equivalent) in the presence of triethylamine (1 equivalent) in DMF at room temperature for 18-20 hrs. The title compound was obtained in 9% yield together with l-acetyl-3-(3-nitrobenzylidene)-2,5-piperazinedione (66% yield). Characterising data are set out in Example 14.

Reference Example 3: Preparation of 1-acetyl-3-(4-N,N-dimethylaminobenzylidine)-2,5 -piperazinedione

1,4-Diacetyl-2,5-piperazinedione,(1 equivalent), prepared as described in Reference Example 1, was treated with 4-N,N-dimethylaminobenzaldehyde (1 equivalent) in the presence of Et_3N in DMF at 130°C for 24 hrs. The title compound was obtained in 18% yield

Example 10: Preparation of Compound 86

1-Acetyl-3-(4-dimethylaminobenzylidene)-2,5-piperazinedione (1 equivalent) as described in Reference Example 3 was treated with 4-acetamidobenzaldehyde (1 equivalent) in the presence of Cs_2CO_3 (1 equivalent) in DMF at 80°C for 2-6 hours. The title compound was obtained in 56% yield. Characterising data are set out in Example 14.

Example 14: Interconversions of compounds of formula A

(i) Compound 31, prepared as described in Example 4, was treated with aqueous lithium hydroxide in a mixture of MeOH and THF at room temperature for 2-3 hrs to give compound 33 in 91% yield.

(ii) Compound 61, prepared as described in Example 3, was treated with aqueous lithium hydroxide in a mixture of MeOH and THF at room temperature for 3 hours to give compound 64 in 57% yield.

(iii) Compound 96, prepared as described in Example 3, was treated with aqueous sodium hydroxide in THF at room temperature for 4 hours to give compound 97 in 54% yield.

(iv) Compound 37, prepared as described in Example 5, was treated with aqueous sodium hydroxide in THF at room temperature for 8 hrs to give compound 36 in 30% yield

(v) Compound 56, prepared as described in Example 5, was treated with trifluoroacetic acid in CH_2Cl_2 at room temperature for 12 hrs to give compound 67 in 96% yield.

(vi) Compound 87, prepared as described in Example 5, was treated with aqueous sodium hydroxide in THF at room temperature for 4 hours to give compound 88 in 69% yield.

(vii) Compound 65, prepared as described in Example 4 was hydrogenated over 10% palladium on carbon as

catalyst in CH_2Cl_2 in the presence of a few drops of trifluoroacetic acid to give compound 39 in 38% yield. Under the same conditions of hydrogenation compound 74 was converted into compound 30 in 95% yield.

(viii) Compound 93, prepared as described in Example 3, was hydrolysed by treatment with aqueous sodium hydroxide in a mixture of MeOH and THF at room temperature for 18 hours to give compound 101 in 72% yield.

(ix) Compound 58, prepared as described in Example 7, was hydrolysed by treatment with aqueous sodium hydroxide in THF at room temperature for 3 hours to give compound 104 in 90% yield.

Characterising data for all compounds prepared in this Example are provided in Example 14.

Example 12: Preparation of Compound 27

1-Acetyl-3-(4-methoxybenzylidene)-2,5-piperazinedione (1 equivalent), compound (9) in Reference Example 1, was treated with 2-naphthaldehyde (1 equivalent) in the presence of Cs_2CO_3 (1.0-1.1 equivalents) in DMF at 80-100°C for 1-6 hours. The title compound was obtained in 84% yield.

Characterising data are provided in Example 14.

Example 13: Preparation of Salts

Compound 98, the hydrochloride salt of compound 102, was prepared by treatment of a solution of compound 102 in THF with 2 molar hydrochloric acid followed by sonication until a clear sdlution was obtained. The solvent was then removed in vacuo and the residual solution was freeze-dried to give compound 98.

Compound 99 was prepared by bubbling HCl gas through a solution of the corresponding free base in THF, followed by evaporation to dryness.

Characterising data are provided in Example 14.

Example 14: Characterization of compounds of formula A

The compounds prepared in the preceding Examples, were characterised by mass spectroscopic, microanalytical, proton nuclear magnetic resonance and, in some cases, infra-red techniques. The results are set out in Table 2:

TABLE 2

Nº	Mol. Formula (M. Wt)	Mass spec m/z, mass, intensity (mode)	^{1}H nmr Solvent δ all 400 MHz	Microanalysis				Infra-red
				Calc		Found		cm^{-1}
21	$C_{18}H_{12}N_2O_2Cl_2$	359, MH^+, 100%; 376, MNH_4^+, 15%; 363, 10%; 362, 10%; 361, 60%; 323, 40% (DCI, NH_3)	d_6-DMSO 7.6-7.30 (m,8H), 6.81 (s, 1H), 6.60 (s, 1H)	C H N Cl	60.19 3.37 7.80 19.74	59.33 3.44 7.55 19.22	59.37 3.68 7.48 19.40	3200, 3050, 1680, 1620, 1400, 1370
22	$C_{18}H_{14}O_2N_2$ (290) mixture of isomers	291, MH^+ (DCI, NH_3)	d_6-DMSO 6.54 (1H, s), 6.71 (1H, s), 6.80 (2H, s), 7.20-7.60 (20H, m), 10.17 (2H, broad singlet), 10.80 (0.5H, broad singlet)	C H N	74.47 4.86 9.65	74.39 4.78 9.68	74.20 4.75 9.60	
23	$C_{20}H_{16}N_2O_4$	348 (M^+, 23%); 306, 100% (EI)	$CDCl_3$ + CF_3CO_2D 2.40 (3H, s), 7.25 (2H, d, J=7Hz), 7.29 (1H, s), 7.40-7.51 (8H, m)	C H N	68.96 4.63 8.04	69.05 4.56 8.15	69.08 4.57 8.15	1620, 1690, 1760, 3200

24	$C_{18}H_{13}N_3O_4$ (335)	336, MH^+, 100%; 353, MNH_4^+, 10%; 306, 20%; 291, 70% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 8.30-8.26 (m, 2H), 7.76-7.67 (m, 2H), 7.53-7.43 (m, 5H), 7.32 (s, 1H), 7.26 (s, 1H)	C H N	64.48 3.91 12.53	65.06 3.93 12.19	65.03 3.98 12.20	
25	$C_{20}H_{18}N_2O_3$ (334)	335, MH^+, 100%; 305, 10%; 291, 20%; 277, 10%; 161, 20% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 7.49-7.39 (m, 7H), 7.20 (d, 2H), 7.00 (d, 2H), 4.11 (q, 2H), 1.45 (t, 3H)	C H N	71.84 5.43 8.38	71.83 5.35 8.38	71.95 5.36 8.41	
26	$C_{21}H_{19}N_3O_4$ (377)	279, 10%; 378 MH^+; 395, MNH_4^+, 50% (DCI/NH_3)	$CDCl_3$+CF_3CO_2D 7.60 (1.62H, d), 7.55 (0.38 H, d), 7.50 (3.55 H, m), 7.45 (0.45H, d), 7.28 (1H, s), 7.22 (1H, s), 7.05 (2H, d), 3.90 (3H, s), 2.38 (2.5H, s), 2.25 (0.5H, s)	C H N	66.83 5.07 11.13	66.77 5.04 11.07	66.94 4.96 11.10	
27	$C_{23}H_{18}N_2O_2$ (370)	371, MH^+; 388, MNH_4^+, 2% (DCI/NH_3)	$CDCl_3$+CF_3CO_2D 8.02 (1H, s), 7.95 (2H, m), 7.90 (1H, m), 7.58 (2H, m), 7.50 (1H, dd), 7.48 (2H, d), 7.40 (1H, s), 7.25 (1H, s), 7.05 (2H, d), 3.90 (3H, s)	C H N	74.58 4.90 7.56	74.48 4.86 7.55	74.39 4.93 7.58	

28	$C_{19}H_{15}N_3O_5$ (365)	366, MH^+; 383, MNH_4^+, 80% (DCI/NH_3)	$CDCl_3$+CF_3CO_2D 8.30 (1H, d), 7.77 (1H, m), 7.67 (1H, m), 7.48 (4H, m), 7.25 (1H, s), 7.02 (2H, d), 3.90 (3H, s)	C H N	62.46 4.13 11.50	62.55 4.17 11.60	62.45 4.16 11.50
29	$C_{19}H_{14}N_2O_3Cl_2$	355, 15%; 389, MH^+; 406, MNH_4^+, 2% (DCI/NH_3)	$CDCl_3$+CF_3CO_2D 7.40 (4H, m), 7.35 (1H, pt), 7.25 (1H, s), 7.10 (1H, s), 7.02 (2H, d), 3.90 (3H, s)	C H N	58.63 3.63 7.20	58.40 3.64 7.13	58.41 3.66 7.12
30	$C_{18}H_{15}N_3O_2$ (305)	306, MH^+, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 7.59 (d, 2H), 7.53 (d, 2H), 7.51-7.42 (m, 5H), 7.31 (s, 1H), 7.22 (s, 1H)				
31	$C_{20}H_{16}N_2O_4$ (348)	349, MH^+, 100%; 366, MNH_4^+, 10% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.39 (3H, s), 7.14-7.54 (11H,m)	C H N	68.96 4.63 8.04	69.14 4.63 8.07	69.16 4.63 8.00
32	$C_{20}H_{16}N_2O_4$ (348)	366, MNH_4^+, 38%; 349, MH^+, 100% (DCI/NH_3)	$CDCl_3$ 2.40 (3H, s), 6.90 (1H, s), 7.04 (1H, s), 7.20 (1H, d), 7.30-7.50 (8H, m), 8.12 (1H, bs), 8.19 (1H, bs)	C H N	68.96 4.63 8.04	68.88 4.56 8.30	69.07 4.55 8.30

33	$C_{18}H_{14}N_2O_3$ (306)	324, MNH_4^+, 5%; 307, MH^+, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 6.97-7.50 (11H, m)					
34	$C_{20}H_{17}N_3O_3$ (347)	348, MH^+, 100%; 305, 70%; 227, 30%; 145, 80% (DCI^+) (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 7.61 (d, 2H), 7.55-7.43 (m, 7H), 7.29 (s, 1H), 7.24 (s, 1H), 2.37+2.25 (singlets, 3H,) (2.37-77%, 2.25- 23%)	C H N	69.15 4.93 12.10	68.87 4.73 11.93	68.96 4.86 11.91	
35	$C_{18}H_{12}O_6N_4$ (380)	380, MH^+, 30%; 398, MNH_4^+, 100% (DCI/NH_3)	$CDCl_3$,CF_3CO_2D 8.37-8.34 (m, 4H), 7.83-7.70 (m, 4H), 7.40 (s, 2H)	C H N	56.85 3.18 14.73	56.84 3.04 14.69	56.74 3.05 14.67	
36	$C_{19}H_{16}N_2O_4$ (336)	337, MH^+; 351, MNH_4^+, 5% (DCI/NH_3)	$CDCl_3$+CF_3CO_2D 7.40 (4H, m), 7.22 (2H, d), 7.00 (2H, d), 6.98 (2H, d), 3.90 (3H, s)					
37	$C_{21}H_{18}N_2O_5$ (378)	379, MH^+; 396, MNH_4^+, 40% (DCI/NH_3)	$CDCl_3$+CF_3CO_2D 7.48 (2H, d), 7.44 (2H, d), 7.20 (4H, m), 7.02 (2H, d), 3.90 (3H, s), 2.40 (3H, s)	C H N	66.66 4.79 7.40	66.38 4.71 7.35	66.63 4.71 7.41	

38	$C_{20}H_{17}N_3O_3$ (347)	348, MH^+, 100%; 365, MNH_4^+, 10%; 331, 10%; 306, 10% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 7.70–7.68 (m, 1H), 7.52–7.38 (m, 8H), 7.28 (s, 1H), 7.14 (s, 1H), 2.30+2.08 (singlets, 3H)	C H N	69.15 4.93 12.10	68.21 4.86 11.79	68.47 4.89 11.85
39	$C_{18}H_{15}N_3O_2$ (305)	306, MH^+, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 7.62–7.48 (m, 9H), 7.28 (s, 1H), 7.17 (s, 1H)				
40	$C_{20}H_{13}N_3O_3Cl_2$ (415)	433/435, MNH_4^+, 100%; 416/418, MH^+, 55%; 380, 13% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.36 (3H, s), 7.14 (1H, s), 7.26 (1H, s), 7.34 (1H, m), 7.42 (2H, d), 7.49 (2H, d), 7.60 (2H, d)	C H N	57.71 3.63 10.09	57.51 3.81 10.34	57.55 3.88 10.13
41	$C_{22}H_{21}N_3O_4$ (391)	409, MNH_4^+, 29%; 392, MH^+, 100%; 350, 32% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.02 (3H, s), 3.34 (3H, s), 3.89 (3H, s), 7.01 (2H, d), 7.21 (1H, s), 7.22 (1H, s), 7.33 (2H, d), 7.43 (2H, d), 7.52 (2H, d)	C H N	67.50 5.41 10.74	66.75 5.34 10.57	66.63 5.36 10.52

42	$C_{20}H_{16}N_3O_3Cl$ (381)	399, MNH_4^+, 32%; 401, 32%; 382, MH^+, 100%; 384, 55% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.35 (3H, s), 7.21 (2H, d), 7.49 (2H, d), 7.50 (4H, m), 7.61 (2H, d)	C H N	69.60 5.01 7.73	69.72 4.95 7.79		69.86 4.94 7.79
43	$C_{21}H_{18}N_2O_4$ (362)	380, MNH_4^+, 70%; 363, MH^+, 100%; 303, 44%; 291, 13%; 279, 11% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.19 (3H, s), 5.2 (2H, s), 7.25 (2H, d), 7.40-7.52 (9H, m)	C H N	69.79 5.30 11.63	69.32 5.38 11.29		69.19 5.26 11.13
44	$C_{21}H_{19}N_3O_3$ (361)	379, MNH_4^+, 10%; 362, MH^+, 100%; 319, 10%; 291, 11% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.19 (3H, s), 4.51 (2H, s), 7.21 (2H, s), 7.32-7.52 (9H, m)	C H N	74.47 4.86 9.65	73.95 4.80 9.57		73.92 4.81 9.56
45	$C_{18}H_{14}N_2O_2$ (290)		d_6-DMSO 6.78 (2H, s), 7.35 (2H, t), 7.40 (4H, t), 7.56 (4H, d)	C H N	60.29 4.55 7.03	59.89 4.54 6.90		59.99 4.56 6.96
46	$C_{20}H_{18}N_2O_5S$ (398)	351, 30%; 399, MH^+; 416, MNH_4^+ (DCI/NH_3)	$CDCl_3$ 8.07 (2H, d), 7.65 (2H, d), 7.47 (2H, d), 7.25 (2H), 7.05 (2H, d), 3.90 (3H, s), 3.18 (3H, s)					

47	$C_{23}H_{24}N_2O_4$ (392)	MH$^+$ 393 (DCI/NH_3)	$CDCl_3$+CF_3CO_2D 7.40 (4H, m), 7.20 (2H, s), 7.00 (4H, m), 4.08 (2H, t), 3.88 (3H, s), 1.82 (2H, m), 1.53 (2H, m), 1.00 (3H, t)	C H N	70.39 6.16 7.14	70.06 6.06 7.20	70.13 6.10 7.13
48	$C_{22}H_{22}N_2O_3$ (362)	MH$^+$ 363 (DCI/NH_3)	$CDCl_3$+CF_3CO_2D 7.48 (7H, m), 7.25 (2H, d), 7.00 (2H, d), 4.05 (2H, t), 1.82 (2H, m), 1.48 (2H, m), 0.98 (3H, t)	C H N	72.91 6.12 7.73	72.14 5.79 7.71	72.09 5.99 7.69
49	$C_{22}H_{22}N_2O_4$ (378)	MH$^+$ 379 (DCI/NH_3)	$CDCl_3$+CF_3CO_2D 7.38 (4H, m), 7.18 (2H, s), 6.98 (4H, pt), 4.62 (1H, m), 3.88 (3H, s), 1.38 (6H, d)	C H N	69.83 5.86 7.40	69.85 5.76 7.41	69.90 5.80 7.42
50	$C_{23}H_{24}N_2O_3$ (376)	MH$^+$ 377 (DCI/NH_3)	$CDCl_3$+CF_3CO_2D 7.55 (2H, d), 7.45 (2H, d), 7.40 (2H, d), 7.25 (2H), 7.05 (2H, d), 3.90 (3H, s), 1.35 (9H, s)	C H N	73.38 6.43 7.44	73.21 6.45 7.44	73.29 6.45 7.44

51	$C_{22}H_{22}N_2O_2$	331, MH^+, 10%; 347, MNH_4^+, 364 (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 7.48 (7H, m), 7.39 (2H, d), 7.25 (2H), 1.35 (9H, s)	C 76.28 H 6.40 N 8.09	75.57 6.28 8.04	75.53 6.34 8.04
52	$C_{21}H_{20}N_2O_3$	291, 10%; 349, MH^+ (DCI/NH_3)	$CDCl_3$+CF_3CO_2D 7.45 (7H, m), 7.25 (1H, s), 7.23 (1H, s), 7.02 (2H, d), 4.55 (1H, m), 1.40 (6H, d)	C 72.40 H 5.79 N 8.04	72.30 5.76 8.15	72.42 5.65 8.12
53	$C_{19}H_{15}N_2O_3Br$ (399 ± 1)	399:401 (100:100)%; 321 62% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 3.88 (3H, s), 7.01 (2H, d), 7.19 (1H, s), 7.22 (1H, s), 7.28-7.31 (1H, m), 7.36-7.43 (4H, m), 7.70 (1H, d)	C 57.16 H 3.79 N 7.02 Br 20.01	57.08 3.77 6.94 20.03	56.95 3.78 6.96
54	$C_{18}H_{12}N_2O_2F_2$ (326)	327, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 6.90-7.03 (2H, m), 7.15 (1H, s), 7.31 (1H, s), 7.38-7.52 (6H, m)	C 66.26 H 3.71 N 8.59	66.44 3.74 8.65	66.50 3.72 8.66
55	$C_{18}H_{13}N_2O_2Br$ (369 ± 1)	369:371, (100:100)%; 386:388, (19:19)%; 291, 63% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 7.29-7.33 (2H, m), 7.39-7.53 (8H, m), 7.71 (1H, d)	C 58.56 H 3.55 N 7.59 Br 21.64	58.57 3.45 7.62 21.33	58.28 3.46 7.47 21.35

56	$C_{25}H_{27}N_3O_5$ (449)	467, MNH_4^+, 3%; 450, MH^+, 7%; 449, M^+, 12%; 394, 100%; 351, 14%; 333, 16% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 1.48 (9H, s), 3.90 (3H, s), 4.34 (2H, s), 7.03 (2H, d), 7.21 (1H, s), 7.33-7.47 (6H, m), 7.51 (1H, s)	C H N	66.80 6.05 9.35	66.45 5.97 9.28	66.50 5.94 9.29
57	$C_{21}H_{20}N_2O_3S$ (380)	398, MNH_4^+, 4%; 381, MH^+, 100%; 333, 24% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.02 (3H, s), 3.71 (2H, s), 3.39 (3H, s), 7.02 (2H, d), 7.21 (2H, s), 7.38-7.49 (6H, m)	C H N S	66.30 5.30 7.36 8.43	65.87 5.16 7.32 7.45	65.82 5.14 7.30 7.62
58	$C_{23}H_{21}N_3O_5$ (419)	437, MNH_4^+, 18%; 420, MH^+, 90%; 405, 30%; 360, 100%; 317, 8% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.21 (3H, s), 2.34 (3H, s), 5.21 (2H, s), 7.25 (2H, d), 7.41-7.50 (6H, m), 7.59 (2H, d)				
59	$C_{20}H_{18}N_2O_{25}$ (350)	368, MNH_4^+, 8%; 351, MH^+, 100%; 303, 31%; 291, 8% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.03 (3H, s), 3.72 (2H, s), 7.28 (1H, s), 7.38-7.51 (10H, m)	C H N	68.55 5.18 7.99	67.94 5.00 8.01	67.89 4.99 8.00

60	$C_{21}H_{20}N_2O_5S$ (412)	430, MNH_4^+, 28%; 413, MH^+, 100%; 333, 35% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.96 (3H, s), 3.91 (3H, s), 4.45 (2H, s), 7.08 (2H, d), 7.24 (2H, d), 7.42 (2H, d), 7.51 (4H, m)	C H N S	61.15 4.89 6.79 7.77	60.86 4.83 6.83 7.37	60.83 4.83 6.83 7.47
61	$C_{21}H_{18}N_2O_3S$ (378)	379, MH^+, 100%; 337, 8%; 305, 8% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.39 (3H, s), 4.15 (2H, s), 7.15-7.50 (11H, m)	C H N	66.65 4.79 7.40	66.28 4.71 7.58	66.20 4.74 7.61
62	$C_{20}H_{16}N_2O_4$ (348)	366, $M^+NH_4^+$, 40%; 349, M^+H, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 4.00 (3H, s), 7.25-7.69 (9H, m), 8.09-8.14 (2H, m),				
63	$C_{22}H_{20}N_2O_4S$ (408)	409, M^+H, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.40 (3H, s), 3.87 (3H, s), 4.18 (2H, s), 7.00 (2H, d), 7.16-7.43 (8H, m)				
64	$C_{10}H_{16}N_2O_2S$ (336)	354, $M^+NH_4^+$, 12%; 337, M^+H, 100%; 305, 30% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 3.65 (2H, s), 7.20-7.55 (11H, m)				

65	$C_{18}H_{13}N_3O_4$ (335)	336, MH^+, 100%; 353, MNH_4^+, 20%; 306, 30%; 291, 30% (DCI/NH_3)	$CDCl_3$,CF_3CO_2D 8.31 (1H, d), 7.78 (1H, m), 7.65 (1H, m), 7.55-7.52 (7H m), 7.31 (1H, s)	C H N	67.45 4.47 8.28	67.44 4.37 8.27	67.44 4.32 8.29
66	$C_{24}H_{25}N_3O_4$ (419)	437, MNH_4^+, 5%; 420, MH^+, 6%; 381, 17%; 364, 100%; 318, 13%; 303, 9%; 291, 32% (DCI/NH_3)	d_6-DMSO 1.40 (9H, s), 4.12 (2H, d), 6.77 (2H, d), 7.22-7.56 (9H, m)	C H N	68.72 6.01 10.02	68.83 5.89 9.81	68.80 5.85 9.83
67	$C_{20}H_{19}N_3O_3$ (349)	350, MH^+, 12%; 349, M^+, 13%; 333, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 3.92 (3H, s), 4.32 (2H, s), 7.05 (2H, d), 7.24 (2H), 7.45 (2H, d), 7.52 (4H, s)				
68	$C_{26}H_{28}N_4O_5$ (476)	494, MNH_4^+, 10%; 477, MH^+, 18%; 476, M^+, 17%; 438, 22%; 421, 100%; 405, 9%; 375, 6%; 360, 28% (DCI/NH_3)	d_6-DMSO 2.09 (3H, s), 2.10 (9H, s), 4.12 (2H, d), 6.71 (2H, d), 7.26 (2H), 7.49 (4H, m), 7.61 (2H, d)				

69	$C_{19}H_{14}N_2O_3F_2$ (356)	357, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 3.88 (3H, s), 6.90-7.20 (4H, m), 7.11 (1H, s), 7.22 (1H, s), 7.37-7.44 (3H, m)	C H N	64.04 3.96 7.86	63.47 3.86 7.79	63.36 3.82 7.77
70	$C_{20}H_{15}N_2O_3F_3$ (388)	389, 100; 406, 19% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 3.90 (3H, s), 7.04 (2H, d), 7.23 (1H, s), 7.37-7.47 (4H, m), 7.55 (1H, t), 7.62 (1H, t), 7.80 (1H, d)				
71	$C_{20}H_{16}N_3O_3F$		$CDCl_3$ + CF_3CO_2D 2.36 (3H, s), 7.18-7.30 (4H, m), 7.40-7.50 (4H, m), 7.58 (2H, d)				
72	$C_{20}H_{16}N_3O_3F$ (365)	383, 21%; 366, 100%; 323, 12% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.36 (3H, s), 7.17-7.28 (4H, m), 7.41-7.49 (4H, m) 7.60 (2H, d)				

73	$C_{21}H_{20}N_2O_5$		$CDCl_3$ + CF_3CO_2D 3.90 (6H, s), 3.99 (3H, s), 6.60 (1H, s), 7.01 (2H, d, J=6Hz), 7.19 (2H, m), 7.30 (1H, s), 7.32 (1H, s), 7.40 (2H, d, J=6Hz)	C H N	66.31 5.30 7.36	66.12 5.25 7.35	66.13 5.22 7.33
74	$C_{18}H_{13}N_3O_4$ (335)	336, MH^+, 100%; 353, MNH_4^+, 30%; 20%; 306, 30%; 291, 30% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 8.35 (d, 2H), 7.62 (d, 2H), 7.55-7.42 (m, 5H), 7.36 (s, 1H), 7.28 (s, 1H)	C H N	64.48 3.91 12.53	64.55 3.90 12.41	64.57 3.89 12.41	3250, 1690, 1620, 1570, 1420, 1370
75	$C_{23}H_{25}N_3O_3$	392, MH^+, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.30 (2H, m), 3.01 (6H, s), 3.43 (2H, m), 4.15 (2H, m), 6.96 (2H, d, J=8Hz), 7.23 (1H, s), 7.40-7.55 (8H, m)	C H N	70.57 6.44 10.73	70.28 6.33 10.59	70.46 6.36 10.68	
76	$C_{21}H_{16}N_2O_3S$	396, MNH_4^+, 4%; 379, MH^+, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 7.53-7.34 (10H, m), 7.21 (1H, s), 4.18 (2H, s), 2.42 (3H, s)	C H N	66.65 4.79 7.40	66.79 4.69 7.41	66.82 4.71 7.41	

77	$C_{20}H_{15}N_3O_3S_2$ (383)	401, 100%; 384, 75% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.37 (3H, s), 6.90-7.05 (2H, m), 7.18 (1H, s), 7.27 (1H, s), 7.39-7.50 (3H, m), 7.60 (2H, d)	C H N	62.66 3.94 10.96	62.65 4.11 11.32	62.63 4.11 11.33
78	$C_{21}H_{16}N_3O_3F_3$ (415)	416, 100%; 433, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.37 (3H, s), 7.22 (1H, s), 7.42-7.49 (4H, m), 7.56-7.70 (4H, m), 7.32 (1H, d)	C H N	60.72 3.88 10.12	60.08 4.14 10.84	60.11 4.15 10.87
79	$C_{20}H_{16}N_3O_3Br$ (426±1)	426:428, (41:41)%; 443:445, (100:100)% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.36 (3H, s), 7.22 (1H, s), 7.29-7.35 (2H, m), 7.38-7.49 (4H, m), 7.60 (2H, d), 7.72 (1H, d)	C H N	56.35 3.78 9.86	56.65 3.92 9.97	56.79 3.84 10.01
80	$C_{20}H_{17}N_3O_4$ (363)	351, 10%, MH^+, 364 (DCI/NH_3)	d_6-DMSO 7.98 (1H, bs), 7.90 (2H, d), 7.60 (2H, d), 7.55 (2H, d), 7.40 (1H, bs), 7.00 (2H, d), 6.78 (2H, m), 3.79 (3H, s)	C H N	66.11 4.72 11.56	65.57 4.71 11.32	65.49 4.71 11.31

81	$C_{24}H_{24}N_2O_5$ (420)	336, 20%; 351, 15%; 379, 25%; 421, MH^+, 100%, MNH_4^+, 438, 10% (DCI/NH_3)	$CDCl_3$+CF_3CO_2D 7.48 (2H, d), 7.45 (2H, d), 7.20 (4H, m), 7.02 (2H, d), 3.90 (3H, s), 1.38 (9H, s)
82	$C_{25}H_{25}N_3O_5$ (447)	363, 25%; 406, 15%; 448, MH^+ 100% (DCI/NH_3)	$CDCl_3$+CF_3CO_2D 7.62 (2H, d), 7.48 (4H, m), 7.25 (2H, d), 7.20 (2H, d), 2.35 (3H, s), 1.40 (9H, s)
83	$C_{21}H_{19}N_3O_5$	411, MNH_4^+, 10%; 394, MH^+, 100%; 362, 57% (DCI/NH_3)	d_6-DMSO 3.68 (3H, s), 3.80 (3H, s), 6.57 (1H, s), 6.60 (1H, s), 6.95 (2H, d, J=7Hz), 7.47 (2H, d, J=7Hz), 7.67 (4H, m), 9.68 (1H, br.s), 9.78 (2H, br.s)

84	$C_{19}H_{15}N_2O_4Cl$ (370/372)	371, MH^+, 100%; 373, 30%; 388, MNH_4^+, 45% (DCI/NH_3)	d_6-DMSO 10.08 (s, 2H), 7.52 (d, 2H), 7.45 (d, 1H), 6.98 (d, 2H), 6.90 (d, 1H), 6.80 (dd, 1H), 6.76 (s, 1H), 6.74 (s, 1H), 3.79 (s, 3H)							
85	$C_{18}H_{13}N_2O_3Cl$ (340/342)	341, MH^+, 100%; 343, 30%; 358, MNH_4^+, 5%; 305, 50% (DCI/NH_3)	d_6-DMSO 8.98 (s, 1H), 8.91 (s, 1H), 8.88 (s, 1H), 7.58 (d, 2H), 7.50 (d, 1H), 7.45 (m, 2H), 7.37 (m, 1H), 6.94 (d, 1H), 6.83 (dd, 1H), 6.80 (s, 1H), 6.79 (s, 1H)							
86	$C_{22}H_{22}N_4O_3$ (390)	391, MH^+, 100%; 408, MNH_4^+, 5% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 7.66-7.58 (m, 6H), 7.46 (2H), 7.24 (2H), 3.35 (s, 6H), 2.35 (s, 3H)	C H N	67.68 5.68 14.35	66.97 5.64 14.35			66.70 5.50 14.15	

87	$C_{23}H_{21}N_3O_6$	453, MNH_4^+, 30%; 436, MH^+, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.32 (3H, s), 3.92 (3H, s), 4.89 (2H, s), 7.03 (2H, d, J=6Hz), 7.24 (1H, s), 7.28 (1H, s), 7.46 (2H, d, J=6Hz), 7.50 (2H, d, J=7Hz), 7.64 (2H, d, J=7Hz)
88	$C_{21}H_{19}N_3O_5$	411, MNH_4^+, 51%; 394, MH^+, 100%; 336, 52% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 3.92 (3H, s), 4.57 (2H, br.s), 7.08 (2H, d, J=7Hz), 7.25 (1H, s), 7.28 (1H, s), 7.49 (2H, d, J=7Hz), 7.50 (2H, d, J=7Hz), 7.70 (2H, d, J=7Hz)

89	$C_{24}H_{21}N_3O_2$ (383)	384, MH^+, 100%; 356, 5%; 296, 5% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 8.26 (d, 1H), 8.07 (d, 1H), 7.86 (m, 1H), 7.78 (d, 1H), 7.74 (d, 1H), 7.68 (m, 2H), 7.55-7.45 (m, 5H), 7.29 (s, 1H), 3.55 (s, 6H)	C H N	75.18 5.52 10.96	74.92 5.50 10.99	74.81 5.52 11.02	
90	$C_{20}H_{18}N_2O_4$ (350)	351, M^++1, 100% (EI)	$CDCl_3$ + CF_3CO_2D 3.90 (3H, s, OMe), 3.95 (3H, s, OMe), 6.90-7.50 (10H, m)					
91	$C_{21}H_{20}N_2O_5$ (380)	381, 100% (EI)	$CDCl_3$ + CF_3CO_2D 3.85 (3H, s, OMe), 3.90 (3H, s, OMe), 3.95 (3H, s, OMe), 6.90-7.45 (9H, m)	C H N	66.31 5.30 7.36	66.40 5.27 7.34	66.20 5.16 7.36	
92	$C_{22}H_{21}N_3O_5$ (407)	425, $M^+NH_4^+$, 25%; 408, MH^+, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.35 (3H, s, Ac), 3.90 (3H, s, OMe), 3.95 (3H, s, OMe), 6.90-7.60 (9H, m)	C H N	64.86 5.20 10.31	64.27 5.15 10.54	64.13 5.15 10.53	
93	$C_{21}H_{18}N_2O_5$ (378)	396, $M^+NH_4^+$, 15%; 379, MH^+, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 3.90 (3H, s, Me), 4.75 (2H, s, CH_2), 6.95-7.50 (11H, m)	C H N	66.66 4.79 7.40	66.77 4.80 7.76	66.83 4.82 7.79	

94	$C_{25}H_{25}N_3O_5$ (447)	465, $M^+NH_4^+$, 15%; 448, MH^+, 100%; 416, M^+-OMe, 20% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.00-2.05 (2H, m), 2.43-2.50 (4H, m), 3.75 (3H, s, Me), 4.50 (2H, s, CH_2Ar), 7.25-7.50 (11H, m)	C H N	67.10 5.63 9.39	66.81 5.44 9.46	66.96 5.42 9.50
95	$C_{27}H_{29}N_3O_5$ (475)	493 ($M^+NH_4^+$, 10%; 476, MH^+, 16%; (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 1.30 (3H, t, Me), 1.70-1.75 (4H, m), 2.40-2.45 (4H, m), 4.20 (2H, q), 4.53 (2H, s), 7.25-7.50 (11H, m)	C H N	68.20 6.15 8.84	68.13 5.95 8.88	68.28 6.00 8.91
96	$C_{24}H_{24}N_2O_5$	421, MH^+, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 1.88 (4H, m), 2.50 (2H, m), 3.77 (3H, s), 4.04 (2H, m), 7.00 (2H, d, J=8Hz), 7.21 (1H, s), 7.38-7.53 (8H, m)				
97	$C_{23}H_{22}N_2O_5$	424, MNH_4^+, 2%; 407, MH^+, 100%; 291, 71% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 1.92 (4H, m), 2.55 (2H, m), 4.09 (2H, m), 7.03 (2H, d, J=8Hz), 7.24 (1H, s), 7.29 (1H, s), 7.39-7.55 (7H, m)				

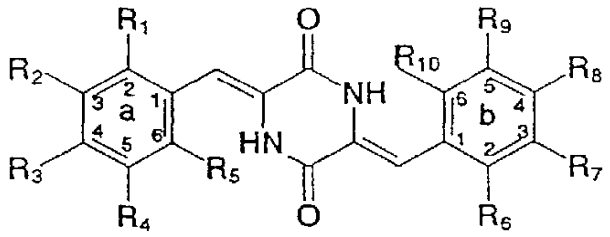
98	$C_{23}H_{26}N_3O_3Cl$	392, $(M-Cl)^+$, 100% (ESI + QIMS)	d_6-DMSO 2.15 (2H, m), 3.20 (2H, m), 3.29 (6H, s), 4.12 (2H, m), 6.77 (1H, s), 6.78 (1H, s), 7.00 (2H, d, J=8Hz), 7.32 (1H, m), 7.40 (2H, m), 7.55 (4H, m), 10.13 (2H, br.s)					
99	$C_{22}H_{24}N_3O_3Cl$	430, 7%; 412, 5%; 478, 100%	d_6-DMSO 2.85 (6H, s, 2xMe), 3.50 (2H, t, CH_2), 4.40 (2H, t, CH_2), 6.75-7.55 (11H, m), 10.15 (2H, br.s, 2xNH), 10.75 (1H, v.br.s., NH)					
100	$C_{26}H_{27}N_3O_6$ (477)	495, M^+NH_4, 13%; 478, MH^+, 100%; 446, 15% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 2.00-2.17 (2H, m), 2.45-2.52 (4H, m), 3.75 (3H,s, Me), 3.88 (3H, s, Me), 4.50 (2H, s), 7.00-7.40 (10H, m)					

101	$C_{20}H_{16}N_2O_5$ (364)	382, $M^+NH_4^+$, 80%; 365, M^++1, 100% (DCI/NH_3)	d_6-DMSO 4.70 (2H, s, OCH_2), 6.75-7.55 (11H, m), 10.12 (1H, br.s., NH), 10.17 (1H, br.s., NH)						
102	$C_{22}H_{23}N_3O_3$ (377)	378, MH^+, 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 3.10 (6H, s, 2xMe), 3.65 (2H, t, CH_2), 4.40 (2H, t, CH_2), 6.95-7.50 (11H, m)						
103	$C_{19}H_{15}N_2O_3F$ (338)	339 100% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 3.91 (3H, s), 7.03 (2H, d), 7.16-7.30 (4H, m), 7.39-7.48 (4H, m)	C H N	67.45 4.47 8.28	67.44 4.37 8.27	67.44 4.32 8.29		
104	$C_{21}H_{19}N_3O_4$ (377)	395, MNH^+, 32%; 378, MH^+, 38% (DCI/NH_3)	d_6-DMSO 2.04 (3H, s), 4.51 (2H, d), 5.18 (1H, t,), 6.72 (1H, s), 6.78 (1H, s), 7.36 (2H, d), 7.50 (4H, m), 7.62 (2H, d)						

105	$C_{19}H_{13}O_2N_3$	316, MH^+, 100%, 201, 53% (DCI/NH_3)	$CDCl_3$ + CF_3CO_2D 7.25 (1H, s), 7.38 (1H, s), 7.43-7.60 (5H, m), 7.61 (2H, d, J=7Hz), 7.85 (2H, d, J=7Hz)	C H N	72.37 4.16 13.33	72.26 4.21 13.21	72.15 4.20 13.16

Claims

1. A compound which is a diketopiperazine of formula (A):

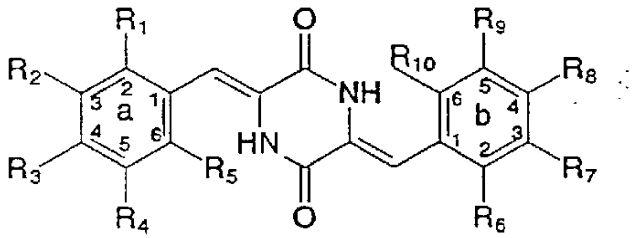


(A)

wherein each of R_1 to R_{10}, which may be the same or different, is independently selected from hydrogen, C_1-C_6 alkyl unsubstituted or substituted by one or more halogen atoms, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halogen hydroxy, nitro, phenyl, cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$ $-NHCOR^{11}$, $NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, CH_2NHCOR^{11}, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ wherein m is 1 or 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ and $-NHCO(CH_2)_nOCOR^{11}$ and $-NHCO(CH_2)_nOR^{11}$ wherein n is 0 or is an integer of from 1 to 6, each of R^{11} and R^{12} is independently H or C_1-C_6 alkyl and R^{13} is C_1-C_6 alkyl; or any of R_1 and R_2, R_3 and R_3, R_3 and R_4 and R_4 and R_5, or R_6 and R_7, R_7 and R_8, R_8 and R_9 and R_9 and R_{10}, form together with the carbon atoms to which they are attached a benzene ring; or a pharmaceutically acceptable salt or ester thereof; with the exception of compounds wherein:

(i) each of rings a and b, which are the same, is unsubstituted or substituted exclusively by 2-chloro, 3-chloro, 4-methyl, 4-acetoxy, 2-carboxy, 4-nitro, 4-amino, 2-bromo, 2-nitro, 4-chloro, 4-methoxy, 4-fluoro, 2-fluoro, 2-acetoxy, 3-acetoxy, 3-nitro, 4-iodo, 4-cyano or 4-dimethylamino;
(ii) each of rings a and b, which are the same, is substituted exclusively by 2,5-dimethyl, 2,5-diacetoxy, 3,4-dimethoxy, 3,4,5-trimethoxy, 2,4,5-trimethoxy, 2,4,5-trimethoxy-3-methyl or 3-carboxy-4-hydroxy;
(iii) one of rings a and b is unsubstituted and the other is substituted exclusively by 4-nitro, 4-methoxy or 2-hydroxy; and
(iv) one of rings a and b is exclusively substituted by 2-carboxy and the other is exclusively substituted by 3-carboxy.

2. A compound which is a diketopiperazine of formula (A):



(A)

wherein ring a bears a different substitution pattern from ring b and each of R_1 to R_{10}, which may be the same or different, is independently selected from hydrogen, C_1-C_6 alkyl unsubstituted or substituted by one or more halogen atoms, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halogen, hydroxy, nitro, optionally substituted phenyl, cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $SO_2N(R^{11}R^{12})$,$-N(R^{11}R^{12})$,$-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$,$-CH_2OCOR^{11}$,$-CH_2NHCOR^{11}$,$-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ wherein m is 1 or 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $NHCO(CH_2)_nOCOR^{11}$ and $-NHCO(CH_2)_nOR^{11}$ wherein n is 0 or an integer of from 1 to 6, each of R^{11} and R^{12} is independently H or C_1-C_6 alkyl and R^{13} is C_1-C_6 alkyl; or any of R_1 and R_2, R_2 and R_3, R_3 and R_4

and R_4 and R_5, or R_6 and R_7 , R_7 and R_8, R_8 and R_9 and R_9 and R_{10}, form together with the carbon atoms to which they are attached a benzene ring which is optionally substituted; or a pharmaceutically acceptable salt or ester thereof; with the exception of compounds wherein one of rings a and b is unsubstituted and the other is substituted exclusively by 4-nitro, 4-methoxy or 2-hydroxy.

3. A compound according to claim 1 or 2 wherein one of R_6 to R_{10} is selected from halogen, alkoxy and - $NHCOR^{11}$ and the other four of R_6 to R_{10} are H.

4. A compound according to any one of the preceding claims wherein R_8 is selected from halogen, alkoxy, and -$NHCOR^{11}$ and R_6, R_7, R_9 and R_{10} are H.

5. A compound according to any one of the preceding claims wherein R_1 and R_2 are independently H, nitro or halogen; R_3 is H, hydroxy, $-O(CH_2)_nN(R^{11}R^{12})$, - $OCOR^{11}$, $-O(CH_2)_nCO_2R^{11}$,- $CH_2NHCO(CH_2)_nCO_2R^{11}$,$C_1$-$C_6$ alkoxy, - $NHCO(CH_2)_nOR^{11}$, $-NHCO(CH_2)OCOR^{11}$, $-N(R^{11}R^{12})$, $-CH_2NHCO_2R^{13}$, - CH_2SR^{11} or $NHCOR^{11}$; R_4 is H, halogen, C_1-C_6 alkoxy, $-CH_2SCOR^{11}$, CH_2SR^{11} or $-CO_2R^{11}$ and R_5 is H, nitro or halogen.

6. A compound according to any one of claims 1 to 4 wherein R_2 and R_3, R_3 and R_4, or R_4 and R_5 form, together with the carbon atoms to which they are attached, an optionally substituted benzene ring.

7. A compound according to any one of claims 1 to 4 wherein R_8 is -NHAc wherein Ac is acetyl, R_1 is H or halogen; R_2 is H, R_3 is halogen, C_1-C_6 alkoxy, $-N(R^{11}R^{12})$ or - $NHCOOR^3$; R_4 is H,; R_5 is halogen or CF_3; and R_6, R_7, R_9 and R_{10} are H.

8. A compound according to any one of claims 1 to 4 wherein R^8 is OME, R_1 is H, nitro or halogen; R_2 is H; R_3 is H, hydroxy, $-OCOR^{11}$, $NHCO(CH_2)_nOCOR^{11}$ or $-NHCOCH_2OR^{11}$; or R_2 and R_3 form, together with the carbon atoms to which they are attached, a benzene ring; R_4 is H; R_5 is H or halogen; and R_6, R_7, R_9 and R_{10} are H.

9. A compound according to any one of claims 1 to 4 wherein R_1, R_6, R_7, R_8, R_9 and R_{10} are H; R_2 is H and R_3 is $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-NHCO(CH_2)_nCO_2R^{11}$, $-O(CH_2)_nCO_2R^{11}$, $-O(CH_2)_nN(R^{11}R^{12})$, or $-N(R^{11}R^{12})$ or R_2 is $-CH_2SCOR^{13}$ or $-CH_2SR^{11}$ and R^3 is H; and R_4 and R_5 are both H or form, together with the carbon atoms to which they are attached, a benzene ring.

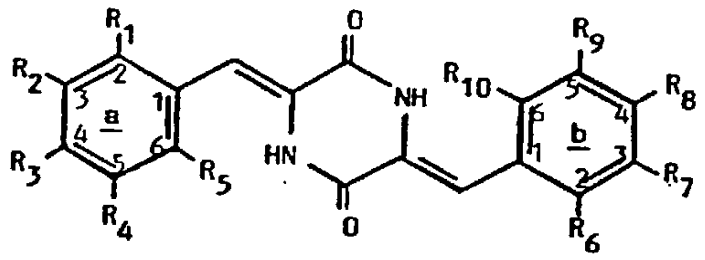
10. A compound according to claim 1 or 2 selected from

(3Z,6Z)-6-Benzylidene-3-(2,6-dichlorobenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Acetoxybenzylidene)-6-benzylidene-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(2-nitrobenzylidene)-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(4-ethoxybenzylidehe)-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(4-cyanobenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Aminobenzylidene)-6-benzylidene-2,5-piperazinedione.
(3Z,6Z)-3-(3-Acetoxybenzylidene)-6-benzylidene-2,5-piperazinedione
(3Z,6Z)-3-(2-Acetoxybenzylidene)-6-benzylidene-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(3-hydroxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-benzylidene-2,5-piperazinedione
(3Z,6Z)-3-(2-Acetamidobenzylidene)-6-benzylidene-2,5-piperazinedione
(3Z,6Z)-3-(2-Aminobenzylidene)-6-benzylidene-2,5-piperazinedione
(3Z,6Z)-3-(4-Acetoxymethylbenzylidene)-6-benzylidene-2,5-piperazinedione
(3Z,6Z)-3-(4-Acetamidomethylbenzylidene)-6-benzylidene-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(3-nitrobenzylidene)-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(4-butoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(4-tert-butylbenzylidene)-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(4-isopropoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(2,4-difluorobenzylidene)-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(2-bromobenzylidene)-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(4-methylthiomethylbenzylidene)-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(3-thioacetoxymethylbenzylidene)-2,5-piperazinedione
3-((3Z,6Z)-6-Benzylidene-2,5-dioxopiperazin-3-ylidene)methylbenzoic acid, methyl ester
-(3Z,6Z)-6-Benzylidene-3-(3-mercaptomethylbenzylidene)-2,5-piperazinedione

(3Z,6Z)-6-Benzylidene-3-(4-tert-butoxycarbonylaminobenzylidene)-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(4-(3-N,N-dimethylaminopropoxy) benzylidene)-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(4-thioacetoxymethylbenzylidene)-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(2-chloro-4-hydroxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-6-Benzylidene-3-(3,4-dimethoxybenzylidene)-2,5-piperazinedione
4-[(3Z,6Z)-6-Benzylidene-2,5-dioxopiperazin-3-ylidene]methylphenoxyacetic acid, methyl ester
4-(4-[(3Z,6Z)-6-Benzylidene-2,5-dioxopiperazin-3-ylidene]methylbenzylcarbamoyl) butanoic acid, methyl ester
4-(4-((3Z,6Z)-6-Benzylidene-2,5-dioxopiperazin-3-ylidene)methylbenzylcarbamoyl)pentanoic acid, methyl ester
5-[4-((3Z,6Z)-6-Benzylidene-2,5-dioxopiperazin-3-ylidene)methylphenoxy]pentanoic acid, methyl ester
5-[4-((3Z,6Z)-6-Benzylidene-2,5-dioxopiperazin-3-ylidene)methylphenoxy]pentanoic acid
(3Z,6Z)-6-Benzylidene-3-(4-(2-N,N-dimethylaminoethoxy)benzylidene)-2,5-piperazinedione, hydrochloride
(3Z,6Z)-6-Benzylidene-3-(4-(2-N,N-dimethylaminoethoxy)benzylidene)-2,5-piperazinedione
4-[(3Z,6Z)-6-Benzylidene-2,5-dioxopiperazin-3-ylidene]methylphenoxyacetic acid
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-6-(4-Methoxybenzylidene)-3-(2-nitrobenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(2,6-Dichlorobenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Hydroxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Acetoxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(4-N-methylacetamidobenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(4-methylsulfonylbenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Butoxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-isopropoxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-methoxybenzylidene)-6-(4-tert-butylbenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(2-Bromobenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-(4-Methoxybenzylidene)-6-(4-tert-butoxycarbonylaminomethylbenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(4-methylthiomethylbenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(4-methylsulfonylmethylbenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(3-thioacetoxymethylbenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Aminomethylbenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(2,4-Difluorobenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(2-trifluoromethylbenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(2,4-Dimethoxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione
4-[(3Z,6Z)-6-(4-Methoxybenzylidene)-2,5-dioxopiperazin-3-ylidene] methylbenzamide
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(4-trimethylacetoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(4-methoxycarbonylaminobenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(2-Chloro-4-hydroxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Acetoxyacetylaminobenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(3,4-Dimethoxybenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione
4-((3Z,6Z)-6-(4-Methoxybenzylidene)-2,5-dioxopiperazin-3-ylidene)-4-methylbenzylcarbamoyl)butanoic acid, methyl ester
(3Z,6Z)-3-(4-Methoxybenzylidene)-6-(2-naphthylmethylene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Hydroxyacetylaminobenzylidene)-6-(4-methoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-benzylidene-2,5-piperazinedione
(3Z,6Z)-3,6-Di-(3-Nitrobenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(2,6-dichlorobenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-chlorobenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-acetoxymethylbenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(2-fluorobenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-fluorobenzylidene)-2,5-piperazinedione
(3Z,6Z)-6-(Benzylidene)-3-(2,4-difluorobenzylidene)-2,5-piperazinedione
(3Z,6Z)-6-(4-Acetamidobenzylidene)-3-(2-trifluoromethylbenzylidene)-2,5-piperazinedione
(3Z,6Z)-6-(4-Acetamidobenzylidene)-3-(2-bromobenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-trimethylacetoxybenzylidene)-2,5-piperazinedione
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-dimethylaminobenzylidene)-2,5-piperazinedione;
(3Z,6Z)-3-(4-Acetamidobenzylidene)-6-(4-tert-butoxycarbonylaminomethylbenzylidene)-2,5-piperazinedione;

and the pharmaceutically acceptable salts thereof.

11. A pharmaceutical or veterinary composition comprising a pharmaceutically or veterinary acceptable carrier or diluent and, as an active principle, a compound which is a diketopiperazine of formula (A):



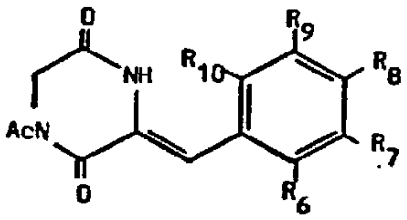
(A)

wherein each of R_1 to R_{10}, which may be the same or different, is independently selected from hydrogen, C_1-C_6 alkyl unsubstituted or substituted by one or more halogen atoms, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halogen, hydroxy, nitro, optionally substituted phenyl, -cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$,$-SO_2N(R^{11}R^{12})$,$-N(R^{11}R^{12})$,$-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$,$-OCOR^{11}$,$-CH_2OCOR^{11}$,$-CH_2NHCOR^{11}$,$-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ wherein m is 1 or 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$,$-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ and $-NHCO(CH_2)_nOR^{11}$ wherein n is 0 or is an integer of from 1 to 6, each of R^{11} and R^{12} is independently H or C_1-C_6 alkyl and R^{13} is C_1-C_6 alkyl; or any of R_1 and R_2, R_2 and R_3, R_3 and R_4 and R_4 and R_5, or R_6 and R_7, R_7 and R_8, R_8 and R_9 and R_9 and R_{10}, form together with the carbon atoms to which they are attached a benzene ring which is optionally substituted; or a pharmaceutically acceptable salt or ester thereof; with the exception of compounds wherein:

(i) each of rings a and b, which are the same, is unsubstitued or substituted exclusively by 2-chloro, 3-chloro, 4-methyl or 4-dimethylamino; and
(ii) each of rings a and b, which are the same, is substituted exclusively by 2,5-dimethyl, 2,4,5-trimethoxy or 3,4,5-trimethoxy.

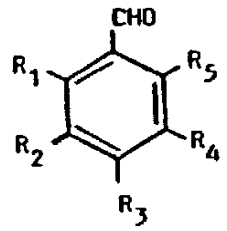
12. A process for preparing a compound of formula (A) as defined in claim 1 or 2, the process comprising:

(a) condensing a compound of formula (I):



(I)

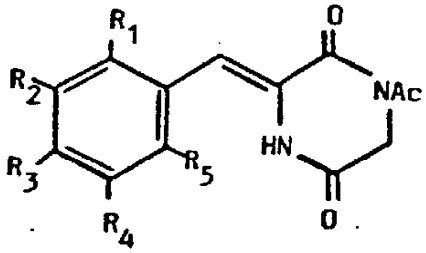
wherein R_6 to R_{10} are as defined in claim 1 and are optionally protected, with a compound of formula (II):



(II)

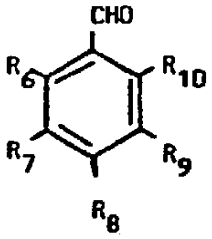
wherein R_1 to R_5 are as defined in claim 1 and are optionally protected, in the presence of a base in an organic solvent; or

(b) condensing a compound of formula (I') :



(I')

wherein R_1 to R_5 are as defined in claim 1 and are optionally protected with a compound of formula (III):

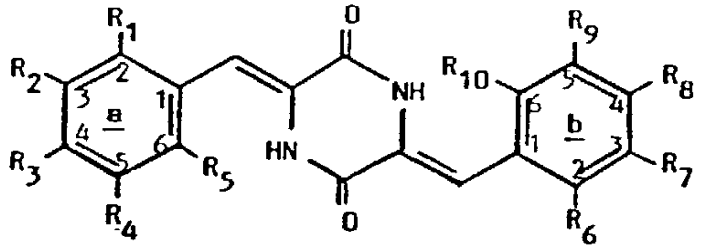


(III)

wherein R_6 to R_{10} are as defined in claim 1 and are optionally protected, in the presence of a base in an organic solvent; and

(c) if required, removing optionally present protecting groups, and/or, if desired, converting one compound of formula A into another compound of formula A, and/or, if desired, converting a compound of formula A into a pharmaceutically acceptable salt or ester thereof, and/or, if desired, converting a salt or ester into a free compound, and/or, if desired, separating a mixture of isomers into the single isomers.

13. A compound for use as an inhibitor of plasminogen activator inhibitor, which compound is a diketopiperazine of formula (A):

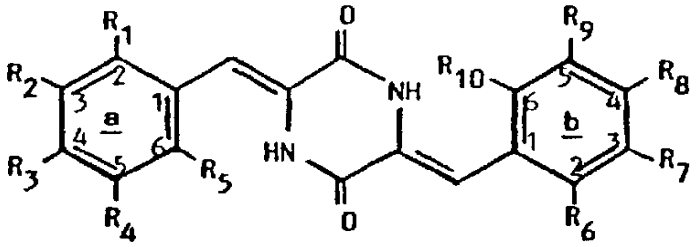


(A)

wherein each of R_1 to R_{10}, which may be the same or different, is independently selected from hydrogen, C_1-C_6 alkyl unsubstituted or substituted by one or more halogen atoms, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halogen, hydroxy, nitro, optionally substituted phenyl, cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ wherein m is 1 or 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$,$-NHCOCF_3$, $-NHCO(CH_2)_nCOR^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ and $-NHCO(CH_2)_nOR^{11}$ wherein n is O or an integer of from 1 to 6, each of R^{11} and R^{12} is independently H or C_1-C_6 alkyl and R^{13} is C_1-C_6 alkyl; or any of R_1 and R_2, R_2 and R_3, R_3 and R_4 and R_4 and R_5, or R_6 and R_7, R_7 and R_8, R_8 and R_9 and R_9 and R_{10}, form together with the carbon atoms to which they are attached a benzene ring which is optionally substituted; or-a pharmaceutically acceptable salt or ester thereof; with the exception of compounds wherein:

(i) each of rings a and b, which are the same, is unsubstituted or substituted exclusively by 2-chloro, 3-chloro, 4-methyl or 4-dimethylamino; and
(ii) each of rings a and b, which are the same, is substituted exclusively by 2,5-dimethyl, 2,4,5-trimethoxy or 3,4,5-trimethoxy.

14. Use of a diketopiperazine of formula (A):

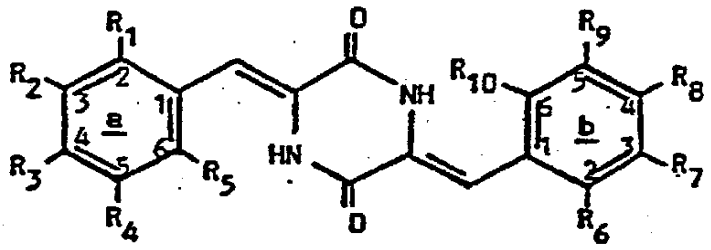


(A)

wherein each of R_1 to R_{10}, which may be the same or different, is independently selected from hydrogen, C_1-C_6 alkyl unsubstituted or substituted by one or more halogen atoms, C_1-C_6 alkoxy, C_1-C_6 alkylthio, halogen, hydroxy, nitro, optionally substituted phenyl, cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$,$-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$,$-COCR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ wherein m is 1 or 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$,$-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ and $-NHCO(CH_2)_nOR^{11}$ wherein n is O or an integer of from 1 to 6, each of R^{11} and R^{12} is independently H or C_1-C_6 alkyl and R^{13} is C_1-C_6 alkyl; or any of R_1 and R_2, R_2 and R_3, R_3 and R_4 and R_4 and R_5, or R_6 and R_7, R_7 and R_8, R_8 and R_9 and R_9 and R_{10}, form together with the carbon atoms to which they are attached a benzene ring which is optionally substituted; or a pharmaceutically acceptable salt or ester thereof; in the manufacture of a medicament for use as an inhibitor of plasminogen activator inhibitor.

Patentansprüche

1. Verbindung, die ein Diketopiperazin der Formel (A) ist:



(A)

in der jeder von R_1 bis R_{10}, die gleich oder verschieden sein können, unabhängig ausgewählt ist aus Wasserstoff, C_1 bis C_6 Alkyl, das unsubstituiert oder mit einem oder mehreren Halogenatomen substituiert ist, C_1 bis C_6 Alkoxy, C_1 bis C_6 Alkylthio, Halogen, Hydroxy, Nitro, Phenyl, -Cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$, worin m 1 oder 2 ist, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ und $-NHCO(CH_2)_nOCOR^{11}$ und $-NHCO(CH_2)_nOR^{11}$, wobei n 0 oder eine ganze Zahl von 1 bis 6 ist, jeder von R^{11} und R^{12} unabhängig H oder C_1 bis C_6 Alkyl und R^{13} C_1 bis C_6 Alkyl ist, oder einer von R_1 und R_2, R_2 und R_3, R_3 und R_4 und R_4 und R_5, oder R_6 und R_7, R_7 und R_8, R_8 und R_9 und R_9 und R_{10}, zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen Benzolring bilden; oder ein pharmazeutisch verträgliches Salz oder Ester davon, mit der Ausnahme von Verbindungen, bei denen:

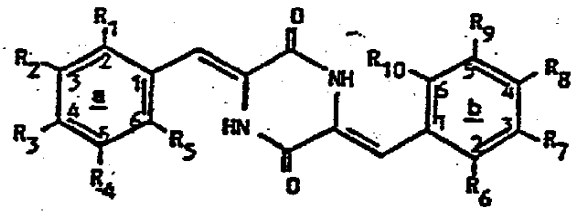
(i) jeder der Ringe a und b, die dieselben sind, unsubstituiert ist oder ausschließlich durch 2-Chloro, 3-Chloro, 4-Methyl, 4-Acetoxy, 2-Carboxy, 4-Nitro, 4-Amino, 2-Bromo, 2-Nitro, 4-Chloro, 4-Methoxy, 4-Fluoro, 2-Fluoro, 2-Acetoxy, 3-Acetoxy, 3-Nitro, 4-Iodo, 4-Cyano oder 4-Dimethylamino substituiert sind;

(ii) jeder der Ringe a und b, die dieselben sind, ausschließlich mit 2,5-Dimethyl, 2,5-Diacetoxy, 3,4-Dimethoxy, 3,4,5-Trimethoxy, 2,4,5-Trimethoxy, 2,4,5-Trimethoxy-3-methyl oder 3-Carboxy-4-hydroxy substituiert ist;

(iii) einer der Ringe a und b unsubstituiert ist und der andere ausschließlich mit 4-Nitro, 4-Methoxy oder 2-Hydroxy substituiert ist, und

(iv) einer der Ringe a und b ausschließlich durch 2-Carboxy und der andere ausschließlich durch 3-Carboxy substituiert ist.

2. Verbindung, die ein Diketopiperazin der Formel (A) ist:



(A)

in der Ring a ein von Ring b verschiedenes Substitutionsmuster trägt und jeder von R1 bis R10, die dieselben oder verschieden sein können, unabhängig ausgewählt ist aus Wasserstoff, C1 bis C6 Alkyl, unsubstituiert oder mit einem oder mehreren Halogenatomen substituiert, C1 bis C6 Alkoxy, C1 bis C6 Alkylthio, Halogen, Hydroxy, Nitro, optional substituiertes Phenyl, Cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, SO_2R^{13}, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$, wobei m 1 oder 2 ist,

$-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ und $-NHCO(CH_2)_nOR^{11}$, wobei n 0 oder eine ganze Zahl von 1 bis 6 ist, jeder von R^{11} und R^{12} unabhängig H oder C_1 bis C_6 Alkyl ist und R^{13} C_1 bis C_6 Alkyl, oder einer von R_1 und R_2, R_2 und R_3, R_3 und R_4 und R_4 und R_5, oder R_6 und R_7, R_7 und R_8, R_8 und R_9 und R_9 und R_{10} zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen Benzolring bilden, der optional substituiert ist, oder ein pharmazeutisch verträgliches Salz oder Ester davon; mit der Ausnahme von Verbindungen, bei denen einer der Ringe oder a oder b unsubstituiert ist und der andere ausschließlich mit 4-Nitro, 4-Methoxy oder 2-Hydroxy substituiert ist.

3. Verbindung gemäß Anspruch 1 oder 2, bei der einer von R_6 bis R_{10} ausgewählt ist aus Halogen, Alkoxy und $-NHCOR^{11}$ und die anderen vier von R_6 bis R_{10} H sind.

4. Verbindung gemäß einem der vorhergehenden Ansprüche, wobei R_8 ausgewählt ist aus Halogen, Alkoxy und $-NHCOR^{11}$ und R_6, R_7, R_9 und R_{10} H sind.

5. Verbindung gemäß einem der vorhergehenden Ansprüche, worin R_1 und R_2 unabhängig H, Nitro oder Halogen sind, R_3 H ist, Halogen, $-O(CH_2)_nN(R^{11}R^{12})$, $-OCOR^{11}$, $-O(CH_2)_nCO_2R^{11}$, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, C_1 bis C_6 Alkoxy, $-NHCO(CH_2)_nOR^{11}$, $-NHCO(CH_2)OCOR^{11}$, $-N(R^{11}R^{12})$, $-CH_2NHCO_2R^{13}$, $-CH_2SR^{11}$ oder $-NHCOR^{11}$, R_4 H, Halogen, C_1 bis C_6 Alkoxy, $-CH_2SCOR^{11}$, CH_2SR^{11} oder $-CO_2R^{11}$ und R_5 H, Nitro oder Halogen ist.

6. Verbindung gemäß einem der Ansprüche 1 bis 4, bei der R_2 und R_3, R_3 und R_4 oder R_4 und R_5 zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen optional substituierten Benzolring bilden.

7. Verbindung gemäß einem der Ansprüche 1 bis 4, in der R_8 -NHAc ist, wobei Ac Acetyl ist, R_1 H oder Halogen, R_2 H, R_3 Halogen, C_1 bis C_6 Alkoxy, $-N(R^{11}R^{12})$ oder $-NHCOOR^{13}$, R_4 H, R_5 Halogen oder CF_3 und R_6, R_7, R_9 und R_{10} H sind.

8. Verbindung gemäß einem der Ansprüche 1 bis 4, bei der R_8 OME ist, R_1 H, Nitro oder Halogen, R_2 H, R_3 H, Hydroxy, $-OCOR^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ oder $-NHCOCH_2OR^{11}$ oder R_2 und R_3 zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen Benzolring bilden, R_4 H ist, R_5 H oder Halogen, und R_6, R_7, R_9 und R_{10} H.

9. Verbindung gemäß einem der Ansprüche 1 bis 4, bei der R_1, R_6, R_7, R_8, R_9 und R_{10} H sind, R_2 H und R_3 $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-NHCO(CH_2)_nCO_2R^{11}$, $-O(CH_2)_nCO_2R^{11}$, $-O(CH_2)_nN(R^{11}R^{12})$, $-N(R^{11}R^{12})$, oder R_2 $-CH_2SCOR^{13}$, $-CH_2SR^{11}$ ist und R_3 H, und R_4 und R_5 beide H sind oder zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen Benzolring bilden.

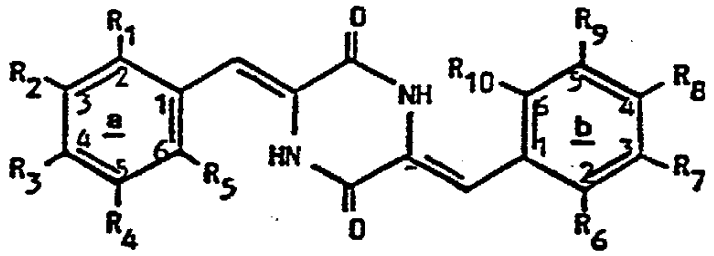
10. Verbindung gemäß Anspruch 1 oder 2, ausgewählt aus

(3Z,6Z)-6-Benzyliden-3-(2,6-dichlorbenzyliden)-2,5-piperazindion,
(3Z,6Z)-3-(4-Acetoxybenzyliden)-6-benzyliden-2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(2-nitrobenzyliden)-2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(4-ethoxybenzyliden)2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(4-cyanobenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Aminobenzyliden)-6-benzyliden-2,5-piperazindion
(3Z,6Z)-3-(3-Acetoxybenzyliden)-6-benzyliden-2,5-piperazindion
(3Z,6Z)-3-(2-Acetoxybenzyliden)-6-benzyliden-2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(3-hydroxybenzyliden)2,5-piperazindion
(3Z,6Z)-3-(4-Acetamidobenzyliden)-6-benzyliden-2,5-piperazindion
(3Z,6Z)-3-(2-Acetamidobenzyliden)-6-benzyliden-2,5-piperazindion
(3Z,6Z)-3-(2-Aminobenzyliden)-6-benzyliden-2,5-piperazindion
(3Z,6Z)-3-(4-Acetoxymethylbenzyliden)-6-benzyliden-2,5-piperazindion
(3Z,6Z)-3-(4-Acetaminomethylbenzyliden)-6-benzyliden-2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(3-nitrobenzyliden)-2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(4-butoxybenzyliden)-2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(4-tert-butylbenzyliden)2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(4-isopropoxybenzyliden)-2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(2,4-difluorbenzyliden)-2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(2-Bromobenzyliden)-2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(4-methylthiomethylbenzyliden)-2,5-piperazindion

(3Z,6Z)-6-Benzyliden-3-(3-thioacetoxymethylbenzyliden)-2,5-piperazindion
3-((3Z,6Z)-6-Benzyliden-2,5-dioxopiperazin-3-yliden)methylbenzoesäuremethylester
(3Z,6Z)-6-Benzyliden-3-(3-mercaptomethylbenzyliden)-2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(4-tert-butoxycarbonylaminobenzyliden)-2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(4-(3-N,N,-dimethylaminopropoxy)benzyliden)-2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(4-thioacetoxymethylbenzyliden)-2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(2-chloro-4-hydroxybenzyliden)-2,5-piperazindion
(3Z,6Z)-6-Benzyliden-3-(3,4-dimethoxybenzyliden)-2,5-piperazindion
4-[(3Z,6Z)-6-Benzyliden-2,5-dioxopiperazin-3-yliden]methylphenoxyessiqsäuremethylester
4-(4-[(3Z,6Z)-6-Benzyliden-2,5-dioxopiperazin-3-yliden]methylbenzylcarbamoyl)butansäuremethylester
4-(4-((3Z,6Z)-6-Benzyliden-2,5-dioxopiperazin-3-yliden)methylbenzylcarbamoyl)pentansäuremethylester
5-[4-(3Z,6Z)-6-Benzyliden-2,5-dioxopiperazin-3-yliden)methylphenoxy]pentansäuremethylester
5-[4-(3Z,6Z)-6-Benzyliden-2,5-dioxopiperazin-3-yliden)methylphenoxy]pentansäure
(3Z,6Z)-6-Benzyliden-3-(4-(2-N,N-dimethylaminoethoxy)benzyliden)-2,5-piperazindionhydrochlorid
(3Z,6Z)-6-Benzyliden-3-(4-(2-N,N-dimethylaminoethoxy)benzyliden)-2,5-piperazindion
4-[(3Z,6Z)-6-Benzyliden-2,5-dioxopiperazin-3-yliden]methylphenoxyessigsäure
(3Z,6Z)-3-(4-Acetamidobenzyliden)-6-(4-methoxybenzyliden)-2,5-piperazindion
(3Z,6Z)-6-(4-Methoxybenzyliden)-3-(2-nitrobenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(2,6-Dichlorbenzyliden)-6-(4-methoxybenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Hydroxybenzyliden)-6-(4-methoxybenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Acetoxybenzyliden)-6-(4-methoxybenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Methoxybenzyliden)-6-(4-N-methylacetamidobenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Methoxybenzyliden)-6-(4-methylsulfonylbenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Butoxybenzyliden)-6-(4-methoxybenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Isopropoxybenzyliden)-6-(4-methoxybenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-methoxybenzyliden)-6-(4-tert-butylbenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(2-Brombenzyliden)-6-(4-methoxybenzyliden)-2,5-piperazindion
(3Z,6Z)-(4-Methoxybenzyliden)-6-(4-tert-butoxycarbonylaminomethylbenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Methoxybenzyliden)-6-(4-methylthiomethylbenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Methoxybenzyliden)-6-(4-methylsulfonylmethylbenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Methoxybenzyliden)-6-(3-thioacetoxymethylbenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Aminomethylbenzyliden)-6-(4-methoxybenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(2,4-Difluorbenzyliden)-6-(4-methoxybenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Methoxybenzyliden)-6-(2-triflourmethylbenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(2,4-Dimethoxybenzyliden)-6-(4-methoxybenzyliden)-2,5-piperazindion
4-[(3Z,6Z)-6-(4-Methoxybenzyliden)-2,5-dioxopiperazin-3-yliden]methylbenzamid
(3Z,6Z)-3-(4-Methoxybenzyliden)-6-(4-trimethylacetoxybenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Methoxybenzyliden)-6-(4-methoxycarbonylaminobenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(2-Chloro-4-hydroxybenzyliden)-6-(4-methoxybenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Acetoxyacetylaminobenzyliden)-6-(4-methoxybenzyliden)2,5-piperazindion
(3Z,6Z)-3-(3,4-Dimethoxybenzyliden)-6-(4-methoxybenzyliden)-2,5-piperazindion
4-((3Z,6Z)-6-(4-Methoxybenzyliden)-2,5-dioxopiperazin-3-yliden)-4-methylbenzylcarbamoyl)butansäuremethylester
(3Z,6Z)-3-(4-Methoxybenzyliden)-6-(2-naphthylmethylen)-2,5-piperazindion
(3Z,6Z)-3-(4-Hydroxyacetylaminobenzyliden)-6-(4-methoxybenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Acetamidobenzyliden)-6-benzyliden-2,5-piperazindion
(3Z,6Z)-3,6-Di-(3-Nitrobenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Acetamidobenzyliden)-6-(2,6-dichlorobenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Acetamidbenzyliden)-6-(4-chlorobenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Acetamidobenzyliden)-6-(4-acetoxymethylbenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Acetamidobenzyliden)-6-(2-fluorbenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Acetamidobenzyliden)-6-(4-fluorbenzyliden)-2,5-piperazindion
(3Z,6Z)-6-(Benzyliden)-3-(2,4-difluorbenzyliden)-2,5-piperazindion
(3Z,6Z)-6-(4-Acetamidobenzyliden)-3-(2-trifluormethylbenzyliden)-2,5-piperazindion
(3Z,6Z)-6-(4-Acetamidobenzyliden)-3-(2-brombenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Acetamidobenzyliden)-6-(4-trimethylacetoxybenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Acetamidobenzyliden)-6-(4-dimethylaminobenzyliden)-2,5-piperazindion
(3Z,6Z)-3-(4-Acetamidobenzyliden)-6-(4-tert-butoxycarbonylaminomethylbenzyliden)-2,5-piperazindion

und die pharmazeutisch verträglichen Salze davon.

11. Pharmazeutische oder veterinärmedizinische Zusammensetzung, enthaltend einen pharmazeutisch oder veterinärmedizinisch verträglichen Träger oder Verdünnungsmittel und, als aktiven Bestandteil, eine Verbindung, die ein Diketopiperazin der Formel (A) ist:



(A)

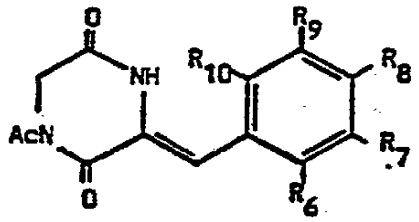
in der jeder von R_1 bis R_{10}, die gleich oder verschieden sein können, unabhängig ausgewählt ist aus Wasserstoff, C_1 bis C_6 Alkyl, das unsubstituiert oder mit einem oder mehreren Halogenatomen substituiert ist, C_1 bis C_6 Alkoxy, C_1 bis C_6 Alkylthio, Halogen, Hydroxy, Nitro, optional substituiertes Phenyl, -Cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$, in der m 1 oder 2 ist, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ und $-NHCO(CH_2)_nOR^{11}$, wobei n 0 oder eine ganze Zahl von 1 bis 6 ist, jeder von R^{11} und R^{12} unabhängig H oder C_1 bis C_6 Alkyl und R^{13} C_1 bis C_6 Alkyl ist; oder einer von R_1 und R_2, R_2 und R_3, R_3 und R_4 und R_4 und R_4 und R_5, oder R_6 und R_7, R_7 und R_8, R_8 und R_9 und R_9 und R_{10} zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen Benzolring bilden der optional substutuiert ist; oder ein pharmazeutisch verträgliches Salz oder ein Ester davon; mit der Ausnahme von Verbindungen, bei denen:

(i) jeder der Ringe a und b, die dieselben sind, unsubstituiert ist oder ausschließlich durch 2-Chloro, 3-Chloro, 4-Methyl, oder 4-Diethylamino substituiert ist; und

(ii) jeder der Ringe a und b, die dieselben sind, ausschließlich mit 2,5-Dimethyl, 2,4,5-Trimethoxy oder 3,4,5-Trimethoxy substituiert ist.

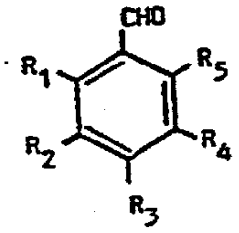
12. Verfahren zur Herstellung einer Verbindung der Formel (A) gemäß Anspruch 1 oder 2, wobei das Verfahren folgende Schritte umfaßt:

(a) Kondensieren einer Verbindung der Formel (I):



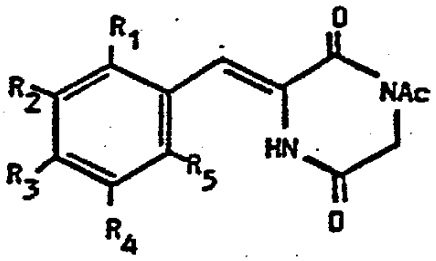
(I)

worin R_6 bis R_{10} wie in Anspruch 1 definiert und optional geschützt sind mit einer Verbindung der Formel (II):



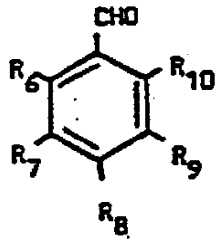
(II)

worin R_1 bis R_5 wie in Anspruch 1 definiert und optional geschützt sind, in der Gegenwart einer Base in einem organischen Lösungsmittel; oder
(b) Kondensieren einer Verbindung der Formel (I'):



(I')

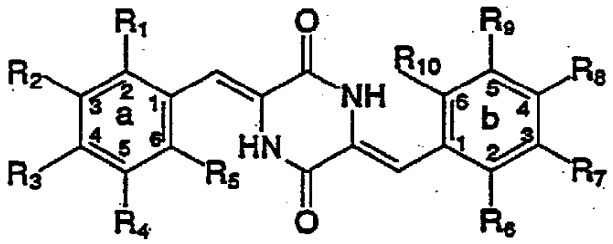
worin R_1 bis R_5 wie in Anspruch 1 definiert und optional mit einer Verbindung der Formel (III) geschützt sind:



(III)

worin R_6 bis R_{10} wie in Anspruch 1 definiert und optional geschützt sind, in der Gegenwart einer Base in einem organischen Lösungsmittel; und
(c) falls erforderlich, Entfernen optional vorhandener Schutzgruppen und/oder, falls gewünscht, Umwandlung einer Verbindung der Formel A in eine andere Verbindung der Formel A und/oder, falls gewünscht, Konvertieren einer Verbindung der Formel A in ein pharmazeutisch akzeptables Salz oder Ester davon und/oder, falls gewünscht, Konvertieren eines Salzes oder Esters in eine freie Verbindung und/oder, falls gewünscht, Trennen einer Mischung von Isomeren in die einzelnen Isomere.

13. Verbindung zur Verwendung als Inhibitor des Plasminogenaktivator-Inhibitors, wobei die Verbindung ein Diketopiperazin der Formel (A) ist:



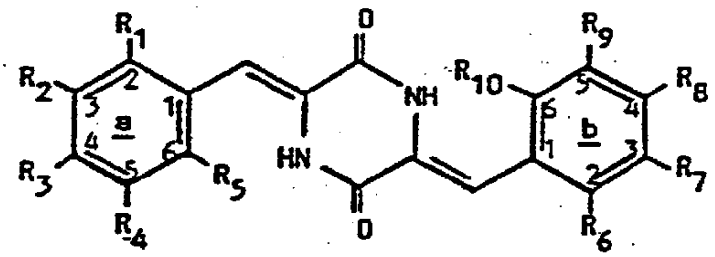
(A)

in der jeder von R_1 bis R_{10}, die gleich oder verschieden sein können, unabhängig ausgewählt ist aus Wasserstoff, C_1 bis C_6 Alkyl, das unsubstituiert oder mit einem oder mehreren Halogenatomen substituiert ist, C_1 bis C_6 Alkoxy, C_1 bis C_6 Alkylthio, Halogen, Hydroxy, Nitro, optional substituiertes Phenyl, -Cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$, worin m 1 oder 2 ist, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ und $-NHCO(CH_2)_nOR^{11}$, wobei n 0 oder eine ganze Zahl von 1 bis 6 ist, jeder von R^{11} und R^{12} unabhängig H oder C_1 bis C_6 Alkyl und R^{13} C_1 bis C_6 Alkyl ist; oder einer von R_1 und R_2, R_2 und R_3, R_3 und R_4 und R_4 und R_5, oder R_6 und R_7, R_7 und R_8, R_8 und R_9 und R_9 und R_{10} zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen Benzolring bilden der optional substutuiert ist; oder eine pharmazeutisch verträgliches Salz oder ein Ester davon; mit der Ausnahme von Verbindungen, bei denen:

(i) jeder der Ringe a und b, die dieselben sind, unsubstituiert oder ausschließlich durch 2-Chloro, 3-Chloro, 4-Methyl, oder 4-Diethylamino substituiert ist; und

(ii) jeder der Ringe a und b, die dieselben sind, ausschließlich mit 2,5-Dimethyl, 2,4,5-Trimethoxy oder 3,4,5-Trimethoxy substituiert ist.

14. Verwendung eines Diketopiperazins der Formel (A):

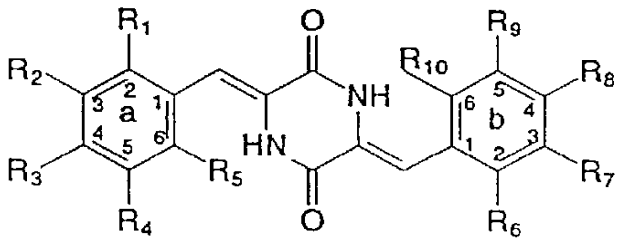


(A)

worin jeder von R_1 bis R_{10}, die dieselben oder verschieden sein können, unabhängig ausgewählt ist aus Wasserstoff, C_1 bis C_6 Alkyl, unsubstituiert oder substituiert durch ein oder mehrere Halogenatome, C_1 bis C_6 Alkoxy, C_1 bis C_6 Alkylthio, Halogen, Hydroxy, Nitro, optional substituiertes Phenyl, Cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$, worin m 1 oder 2 ist, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ und $-NHCO(CH_2)_nOR^{11}$ worin n 0 oder eine ganze Zahl von 1 bis 6 ist, jeder von R^{11} und R^{12} unabhängig H oder C_1 bis C_6 Alkyl ist und R^{13} C_1 bis C_6 Alkyl; oder einer von R_1 und R_2, R_2 und R_3, R_3 und R_4 und R_4 und R_5, oder R_6 und R_7, R_7 und R_8, R_8 und R_9 und R_9 und R_{10} zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen Benzolring bilden, der optional substituiert ist, oder ein pharmazeutisch verträgliches Salz oder Ester davon, zur Herstellung eines Medikaments zur Verwendung als Inhibitor des Plasminogenaktivatorlnhibitors.

Revendications

1. Un composé qui est une dicétopipérazine de formule (A):

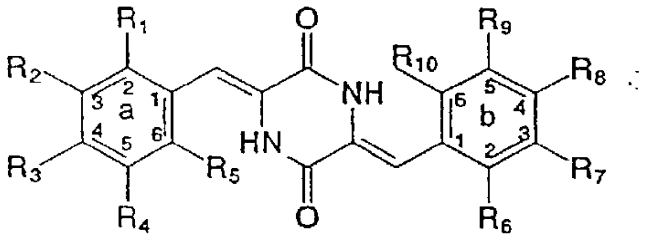


(A)

dans laquelle R_1 à R_{10}, qui peuvent être identiques ou différents, sont chacun indépendamment un atome d' hydrogène, C_1-C_6 alkyle substitué ou non par un ou plusieurs atomes d' halogène, C_1-C_6 alcoxy, C_1-C_6 alkylthio, halogène, hydroxy, nitro, phényle, -cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$ $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ où m est 1 ou 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ et $-NHCO(CH_2)_nOCOR^{11}$ et $-NHCO(CH_2)_nOR^{11}$ où n est 0 ou un entier compris entre 1 et 6, R^{11} et R^{12} sont chacun indépendamment H ou C_1-C_6 alkyle et R^{13} est C_1-C_6 alkyle; ou n' importe lesquels de R_1 et R_2, R_2 et R_3, R_3 et R_4 et R_4 et R_5, ou R_6 et R_7, R_7 et R_8, R_8 et R_9 et R_9 et R_{10}, forment ensemble avec les atomes de carbone auxquels ils sont attachés un noyau benzénique; ou un sel ou un ester pharmaceutiquement acceptable de ce composé; à l'exception des composés dans lesquels:

(i) chacun des noyaux a et b, qui sont identiques, est non substitué ou substitué exclusivement par 2-chloro, 3-chloro, 4-méthyle, 4-acétoxy, 2-carboxy, 4-nitro, 4-amino, 2-bromo, 2-nitro, 4-chloro, 4-méthoxy, 4-fluoro, 2-fluoro, 2-acétoxy, 3-acétoxy, 3-nitro, 4-iodo, 4-cyano ou 4-diméthylamino;
(ii) chacun des noyaux a et b, qui sont identiques, est substitué exclusivement par 2,5-diméthyle, 2,5-diacétoxy, 3,4-diméthoxy, 3,4,5-triméthoxy, 2,4,5-triméthoxy, 2,4,5-triméthoxy-3 -méthyle ou 3-carboxy-4-hydroxy;
(iii) un des noyaux a et b n' est pas substitué et l'autre est substitué exclusivement par 4-nitro, 4-méthoxy ou 2-hydroxy ; et
(iv) un des noyaux a et b est substitué exclusivement par 2-carboxy et 1' autre est substitué exclusivement par 3-carboxy.

2. Un composé qui est une dicétopipérazine de formule (A):



(A)

dans laquelle le noyau a a un mode de substitution différent du noyau b et R_1 à R_{10}, qui peuvent être identiques ou différents, sont chacun indépendamment un atome d' hydrogène, C_1-C_6 alkyle substitué ou non par un ou plusieurs atomes d' halogène, C_1-C_6 alcoxy, C_1-C_6 alkylthio, halogène, hydroxy, nitro, phényle éventuellement substitué, cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$,$-SOR^{13}$, $-SO_2N(R^{11}R^{12})$,$-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$,$-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ où m est 1 ou 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ et $-NHCO(CH_2)_nOR^{11}$ où n est 0 ou un entier

compris entre 1 et 6, R^{11} et R^{12} sont chacun indépendamment H ou C_1-C_6 alkyle et R^{13} est C_1-C_6 alkyle; ou n' importe lesquels de R_1 et R_2, R_2 et R_3, R_3 et R_4 et R_4 et R_5, ou R_6 et R_7, R_7 et R_8, R_8 et R_9 et R_9 et R_{10} forment ensemble avec les atomes de carbone auxquels ils sont attachés un noyau benzénique qui est éventuellement substitué; ou un sel ou un ester pharmaceutiquement acceptable de ce composé ; à l'exception des composés dans lesquels un des noyaux a et b n' est pas substitué et l'autre est substitué exclusivement par 4-nitro, 4-méthoxy ou 2-hydroxy.

3. Un composé selon la revendication 1 ou 2 dans lequel un des radicaux R_6 à R_{10} est choisi parmi un atome d' halogène, un groupe alcoxy et -NHCOR[11] et les quatres autres radicaux R_6 à R_{10} sont H.

4. Un composé selon l'une quelconque des revendications précédentes dans lequel R_8 est choisi parmi un atome d' halogène, un groupe alcoxy, et -NHCOR[11] et R_6, R_7, R_9 et R_{10} sont H.

5. Un composé selon l'une quelconque des revendications précédentes dans lequel R_1 et R_2 sont indépendamment H, nitro ou halogène; R_3 est H, halogène, $-O(CH_2)_nN(R^{11}R^{12})$, $-OCOR^{11}$, $-O(CH_2)_nCO_2R^{11}$, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, C_1-C_6 alcoxy, $-NHCO(CH_2)_nOR^{11}$, $-NHCO(CH_2)OCOR^{11}$, $-N(R^{11}R^{12})$, $-CH_2NHCO_2R^{13}$, $-CH_2SR^{11}$ ou $NHCOR^{11}$; R_4 est H, halogène, C_1-C_6 alcoxy, $-CH_2SCOR^{11}$, CH_2SR^{11} ou $-CO_2R^{11}$ et R_5 est H, nitro ou halogène.

6. Un composé selon une quelconque des revendications 1 à 4 dans lequel R_2 et R_3, R_3 et R_4, ou R_4 et R_5 forment ensemble avec les atomes de carbone auxquels ils sont attachés, un noyau benzénique éventuellement substitué.

7. Un composé selon l'une quelconque des revendications 1 à 4 dans lequel R_8 est -NHAc où Ac est acétyle, R_1 est H ou halogène; R_2 est H, R_3 est halogène, C_1-C_6 alcoxy, $-N(R^{11}R^{12})$ ou $-NHCOOR^{13}$; R_4 est H; R_5 est halogène ou CF_3; et R_6, R_7, R_9 et R_{10} sont H.

8. Un composé selon l'une quelconque des revendications 1 à 4 dans lequel R^8 est OMe, R_1 est H, nitro ou halogène; R_2 est H; R_3 est H, hydroxy, $-OCOR^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ ou $-NHCOCH_2OR^{11}$; ou R_2 et R_3 forment ensemble avec les atomes de carbone auxquels ils sont attachés un noyau benzénique; R_4 est H; R_5 est H ou halogène ; et R_6, R_7, R_9 et R_{10} sont H.

9. Un composé selon l'une quelconque des revendications 1 à 4 dans lequel R_1, R_6, R_7, R_8, R_9 et R_{10} sont H; R_2 est H et R_3 est $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-NHCO(CH_2)_nCO_2R^{11}$, $-O(CH_2)_nCO_2R^{11}$, $-O(CH_2)_nN(R^{11}R^{12})$, ou $-N(R^{11}R^{12})$ ou R_2 est $-CH_2SCOR^{13}$ ou $-CH_2SR^{11}$ et R_3 est H; et R_4 et R_5 sont tous les deux H ou forment ensemble avec les atomes de carbone auxquels ils sont attachés, un noyau benzénique.

10. Un composé selon la revendication 1 ou 2 choisi parmi (3Z, 6Z)-6-Benzylidène-3- (2,6-dichlorobenzylidène)-2,5-pipérazinedione

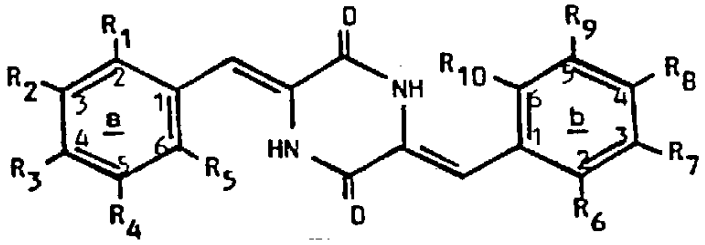
(3Z, 6Z)-3-(4-Acétoxybenzylidène)-6-benzylidène-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(2-nitrobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(4-éthoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(4-cyanobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Aminobenzylidène)-6-benzylidène-2,5-pipérazinedione
(3Z, 6Z)-3-(3-Acétoxybenzylidène)-6-benzylidène-2,5-pipérazinedione
(3Z, 6Z)-3-(2-Acétoxybenzylidène)-6-benzylidène-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(3-hydroxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Acétamidobenzylidène)-6-benzylidène-2,5-pipérazinedione
(3Z, 6Z)-3-(2-Acétamidobenzylidène)-6-benzylidène-2,5-pipérazinedione
(3Z, 6Z)-3-(2-Aminobenzylidène)-6-benzylidène-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Acétoxyméthyibenzylidène)-6-benzylidène-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Acétamidométhylbenzylidène)-6-benzylidène-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(3-nitrobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(4-butoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(4-tert-butylbenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(4-isopropoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(2,4-difluorobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(2-bromobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(4-méthylthiométhylbenzylidène)-2, 5-pipérazinedione

(3Z, 6Z)-6-Benzylidène-3-(3-thioacétoxyméthylbenzylidène)-2,5-pipérazinedione Méthyle ester d' acide 3-((3Z, 6Z)-6-benzylidène-2,5-dioxopipérazin-3-ylidène)méthylbenzoïque
(3Z, 6Z)-6-Benzylidène-3-(3-mercaptométhylbenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(4-tert-butoxycarbonylaminobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(4-(3-N,N-diméthylaminopropoxy)benzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(4-thioacétoxyméthylbenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(2-chloro-4 hydroxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(3,4-diméthoxybenzylidène)-2,5-pipérazinedione Méthyle ester d' acide 4-[(3Z, 6Z)-6-benzylidène-2,5-dioxopipérazin-3-ylidène] méthylphénoxyacétique
Méthyle ester d' acide 4-(4-[(3Z, 6Z)-6-benzylidène-2,5-dioxopipérazin-3 -ylidène] méthylbenzylcarbamoyl) butanoïque
Méthyle ester d' acide 4-(4-((3Z, 6Z)-6-benzylidène-2,5-dioxopipérazin-3-ylidène) méthylbenzylcarbamoyl) pentanoïque
Méthyle ester d' acide 5-[4-((3Z, 6Z)-6-benzylidène-2,5-dioxopipérazin-3-ylidène) méthylphénoxy]pentanoïque
Acide 5-[4-((3Z, 6Z)-6-benzylidène-2,5-dioxopipérazin-3-ylidène) méthylphénoxy] pentanoïque
Chlorhydrate de (3Z, 6Z)-6-benzylidène-3-(4-(2-N,N-diméthylaminoéthoxy)benzylidène)-2, 5-pipérazinedione
(3Z, 6Z)-6-Benzylidène-3-(4-(2-N,N-diméthylaminoéthoxy)benzylidène)-2,5-pipérazinedione
Acide 4-[(3Z, 6Z)-6-benzylidène-2, 5-dioxopipérazin-3 -ylidène] méthylphénoxyacétique
(3Z, 6Z)-3-(4-Acétamidobenzylidène)-6-(4-méthoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-(4-Méthoxybenzylidène)-3-(2-nitrobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(2,6-Dichlorobenzylidène)-6-(4-méthoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Hydroxybenzylidène)-6-(4-méthoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Acétoxybenzylidène)-6-(4-méthoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Méthoxybenzylidène)-6-(4-N-méthylacétamidobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Méthoxybenzylidène)-6-(4-méthylsulfonylbenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Butoxybenzylidène)-6-(4-méthoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Isopropoxybenzylidène)-6-(4-méthoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Méthoxybenzylidène)-6-(4-tert-butylbenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(2-Bromobenzylidène)-6-(4-methoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-(4-Méthoxybenzylidène)-6-(4-tert-butoxycarbonylaminométhylbenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Méthoxybenzylidène)-6-(4-méthylthiométhylbenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Méthoxybenzylidène)-6-(4-méthylsulfonylméthylbenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Méthoxybenzylidène)-6-(3-thioacétoxyméthylbenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Aminométhylbenzylidène)-6-(4-méthoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(2,4-Difluorobenzylidène)-6-(4-méthoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Méthoxybenzylidène)-6-(2-trifluorométhylbenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(2,4-Diméthoxybenzylidène)-6-(4-méthoxybenzylidène)-2,5-pipérazinedione
4-[(3Z, 6Z)-6-(4-Méthoxybenzylidène)-2,5-dioxopipérazin-3-ylidène] méthylbenzamide
(3Z,6Z)-3-(4-Méthoxybenzylidène)-6-(4-triméthylacétoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Méthoxybenzylidène)-6-(4-méthoxycarbonylaminobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(2-Chloro-4-hydroxybenzylidène)-6-(4-méthoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Acétoxyacétylaminobenzylidène)-6-(4-méthoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(3,4-Diméthoxybenzylidène)-6-(4-méthoxybenzylidène)-2,5-pipérazinedione
Méthyle ester d' acide 4-((3Z, 6Z)-6-(4-méthoxybenzylidène)-2, 5-dioxopipérazin-3 -ylidène)-4-méthylbeazylcarbamoyl)butanoïque
(3Z, 6Z)-3(4-Méthoxybenzylidène)-6-(2-naphthylméthylène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Hydroxyacétylaminobenzylidène)-6-(4-méthoxybenzylidéne)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Acétamidobenzylidène)-6-benzylidène-2,5-pipérazinedione
(3Z, 6Z)-3,6-Di-(3-Nitrobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Acétamidobenzylidène)-6-(2,6-dichlorobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Acétamidobenzylidène)-6-(4-chlorobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Acétamidobenzylidène)-6-(4-acétoxyméthylbenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Acétamidobenzylidène)-6-(2-fluorobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3(4-Acétamidobenzylidène)-6-(4-fluorobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-(Benzylidène)-3-(2,4-difluorobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-(4-Acétamidobenzylidène)-3-(2-trifluorométhylbenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-6-(4-Acétamidobenzylidène)-3-(2-bromobenzylidène)-2,5-pipérazinedione

(3Z, 6Z)-3-(4-Acétamidobenzylidène)-6-(4-triméthylacétoxybenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Acétamidobenzylidène)-6-(4-diméthylaminobenzylidène)-2,5-pipérazinedione
(3Z, 6Z)-3-(4-Acétamidobenzylidène)-6-(4-tert-butoxycarbonylaminométhylbenzylidène)-2,5-pipérazinedione;

et les sels pharmaceutiquement acceptables de ce composé.

11. Une composition pharmaceutique ou vétérinaire comprenant un support ou un diluant pharmaceutiquement ou vétérinairement acceptable et, comme principe actif, un composé qui est une dicétopipérazine de formule (A):



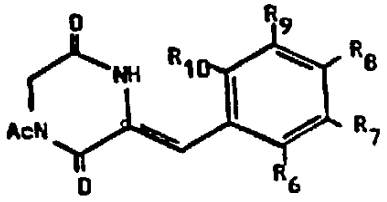
(A)

dans laquelle R_1 à R_{10}, qui peuvent être identiques ou différents, sont chacun indépendamment un atome d' hydrogène, C_1-C_6 alkyle substitué ou non par un ou plusieurs atomes d' halogène, C_1-C_6 alcoxy, C_1-C_6 alkylthio, halogène, hydroxy, nitro, phényle éventuellement substitué, -cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ où m est 1 ou 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-CH_2S(O)_mR^{13}$ où m est 1 ou 2, $CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ et $-NHCO(CH_2)_nOR^{11}$ où n est 0 ou un entier compris entre 1 et 6, R^{11} et R^{12} sont chacun indépendamment H ou C_1-C_6 alkyle et R^{13} est C_1-C_6 alkyle; ou n' importe lesquels de R_1 et R_2, R_2 et R_3, R_3 et R_4 et R_4 et R_5, ou R_6 et R_7, R_7 et R_8, R_8 et R_9 et R_9 et R_{10} forment ensemble avec les atomes de carbone auxquels ils sont attachés un noyau benzénique qui est éventuellement substitué; ou un sel ou un ester pharmaceutiquement acceptable de ce composé ; à l'exception des composés dans lesquels:

(i) chacun des noyaux a et b, qui sont identiques, est non substitué ou substitué exclusivement par 2-chloro, 3-chloro, 4-méthyle ou 4-diméthylamino; et
(ii) chacun des noyaux a et b, qui sont identiques, est substitué exclusivement par 2,5-diméthyle, 2,4,5-triméthoxy ou 3,4,5-triméthoxy.

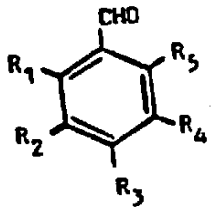
12. Un procédé pour préparer un composé de formule (A) telle que définie dans la revendication 1 ou 2, le procédé comprenant :

(a) la condensation d' un composé de formule (I) ;



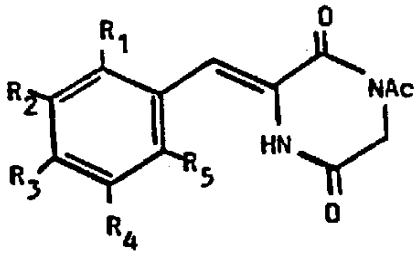
(I)

dans laquelle R_6 à R_{10} sont tels que définis dans la revendication 1 et sont éventuellement protégés, avec un composé de formule (II) :



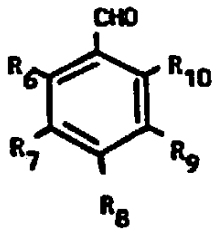
(II)

dans laquelle R_1 à R_5 sont tels que définis dans la revendication 1 et sont éventuellement protégés, en présence d' une base dans un solvant organique ; ou
(b) la condensation d' un composé de formule (I') :



(I')

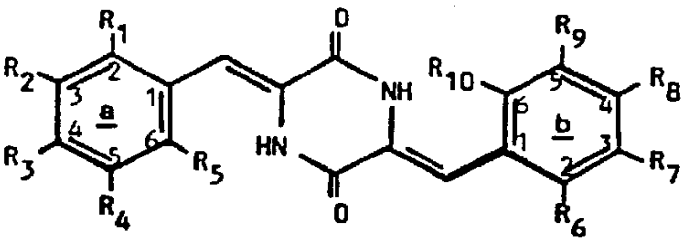
dans laquelle R_1 à R_5 sont tels que définis dans la revendication 1 et sont éventuellement protégés avec un composé de formule (III) :



(III)

dans laquelle R_6 à R_{10} sont tels que définis dans la revendication 1 et sont éventuellement protégés, en présence d' une base dans un solvant organique; et
(c) si nécessaire, l'élimination des groupements protecteurs éventuellement présents, et/ou, si désiré, la conversion d' un composé de formule A en un autre composé de formule A, et/ou, si désiré, la conversion d' un composé de formule A en un sel ou un ester pharmaceutiquement acceptable de ce composé, et/ou, si désiré, la conversion d' un sel ou d'un ester en un composé libre, et/ou, si désiré, la séparation d' un mélange d' isomères pour obtenir chaque isomère.

13. Un composé utilisé comme inhibiteur de l'inhibiteur de l'activateur du plasminogène, lequel composé est une dicétopipérazine de formule (A):



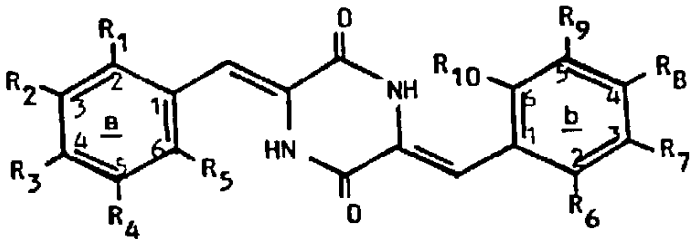
(A)

dans laquelle R_1 à R_{10}, qui peuvent être identiques ou différents, sont chacun indépendamment un atome d' hydrogène, C_1-C_6 alkyle substitué ou non par un ou plusieurs atomes d'halogène, C_1-C_6 alcoxy, C_1-C_6 alkylthio, halogène, hydroxy, nitro, phényle éventuellement substitué, cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $-SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$,$-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ où m est 1 ou 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ et $-NHCO(CH_2)_nOR^{11}$ où n est 0 ou un entier compris entre 1 et 6, R^{11} et R^{12} sont chacun indépendamment H ou C_1-C_6 alkyle et R^{13} est C_1-C_6 alkyle; ou n' importe lesquels de R_1 et R_2, R_2 et R_3, R_3 et R_4 et R_4 et R_5, ou R_6 et R_7, R_7 et R_8, R_8 et R_9 et R_9 et R_{10} forment ensemble avec les atomes de carbone auxquels ils sont attachés un noyau benzénique qui est éventuellement substitué; ou un sel ou un ester pharmaceutiquement acceptable de ce composé ; à l'exception des composés dans lesquels:

(i) chacun des noyaux a et b, qui sont identiques, est non substitué ou substitué exclusivement par 2-chloro, 3-chloro, 4-méthyle ou 4-diméthylamino; et

(ii) chacun des noyaux a et b, qui sont identiques, est substitué exclusivement par 2,5-diméthyle, 2,4,5-triméthoxy, 3,4,5-triméthoxy.

14. Utilisation d' une dicétopipérazine de formule (A):



(A)

dans laquelle R_1 à R_{10}, qui peuvent être identiques ou différents, sont chacun indépendamment un atome d' hydrogène, C_1-C_6 alkyle substitué ou non par un ou plusieurs atomes d' halogène, C_1-C_6 alcoxy, C_1-C_6 alkylthio, halogène, hydroxy, nitro, phényle éventuellement substitué, cyano, $-CH_2OH$, $-CH_2COOH$, $-CO_2R^{11}$, $-NHCOR^{11}$, $-NHSO_2R^{13}$, $-SO_2R^{13}$, $-CON(R^{11}R^{12})$, $-SOR^{13}$, $(SO_2N(R^{11}R^{12})$, $-N(R^{11}R^{12})$, $-O(CH_2)_nN(R^{11}R^{12})$, $-O(CH_2)_nCO_2R^{11}$, $-OCOR^{11}$, $-CH_2OCOR^{11}$, $-CH_2NHCOR^{11}$, $-CH_2NHCOOR^{13}$, $-CH_2SR^{11}$, $-CH_2SCOR^{11}$, $-CH_2S(O)_mR^{13}$ où m est 1 ou 2, $-CH_2NHCO(CH_2)_nCO_2R^{11}$, $-N(R^{11})COR^{12}$, $-NHCOCF_3$, $-NHCO(CH_2)_nCO_2R^{11}$, $-NHCO(CH_2)_nOCOR^{11}$ et $-NHCO(CH_2)_nOR^{11}$ où n est 0 ou un entier compris entre 1 et 6, R^{11} et R^{12} sont chacun indépendamment H ou C_1-C_6 alkyle et R^{13} est C_1-C_6 alkyle; ou n' importe lesquels de R_1 et R_2, R_2 et R_3, R_3 et R_4 et R_4 et R_5, ou R_6 et R_7, R_7 et R_8, R_8 et R_9 et R_9 et R_{10} forment ensemble avec les atomes de carbone auxquels ils sont attachés un noyau benzénique qui est éventuellement substitué; ou un sel ou un ester pharmaceutiquement acceptable de ce composé; dans la fabrication d' un médicament utilisé comme inhibiteur de 1' inhibiteur de l'activateur du plasminogène.